Supplemental Online Content

He L, Wang J, Ping F, et al. Association of glucagon-like peptide-1 receptor agonist use with risk of gallbladder and biliary diseases: a systematic review and meta-analysis of randomized clinical trials. *JAMA Intern Med*. Published online March 28, 2022. doi:10.1001/jamainternmed.2022.0338

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods 1. Data Sources and Search strategies

Example of an online strategy run in Web of Science

#1

TS= ("Glucagon-Like Peptide-1Receptor" OR "glucagon like peptide 1 receptor agonist" OR "glp 1 agonist" OR "glp 1 receptor agonist" OR "glucagon like peptide 1 agonist" OR "glucagon like peptide 1 receptor stimulating agent" OR "long acting glp 1 agonist" OR "long acting glp 1 receptor agonist" OR "long acting glucagon like peptide 1 agonist" OR "long acting glucagon like peptide 1 receptor agonist" OR "dulaglutide" OR "liraglutide" OR "exenatide" OR "albiglutide" OR "semaglutide" OR "lixisenatide")

#2

TS=("randomi?ed trial" OR "clinical trial" OR "randomi?ed" OR "random allocation" OR random* OR "controlled trial" OR "randomized controlled trial")

#3

TS= (retraction of publication or retracted publication)

#4

#2 OR #3

#5

#1 AND #4

eMethods 2. Identifications of the outcomes

We identified the gallbladder or biliary diseases based on the classifications in the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. The biliary diseases were captured with the preferred terms (PTs), which include bile duct stone, bile duct obstruction, bile duct stenosis, biliary colic, biliary fistula, biliary cyst, and cholangitis. The lowest level terms (LLTs) that fell into the PTs listed above were also included.

eTable 1. Eligibility criteria of included studies

	Inclusion criteria	Exclusion criteria
Participants	Adults (≥ 18 or 20 years old); with type 2 diabetes, prediabetes, obesity, overweight, nonalcoholic steatohepatitis, and/or metabolic syndrome	Pregnant women; type 1 diabetes; Participants receiving GLP-1RAs treatments before the trials.
Intervention	Any of the six types of GLP-1RAs, including liragkutide, semaglutide, exenatide, dulaglutide, lixisenatide, albiglutide; GLP-1RAs could be in any dose and frequency; GLP-1RAs could be used as monotherapy or add-on treatments to other interventions.	Co-formulation of fixed-dose combinations of GLP-1RAs other anti-diabetic drugs (e.g., IDegLira is a fixed-ratio combination of insulin degludec and liraglutide)
Comparators	Placebo, non-GLP-1RAs medications; non-pharmaceutical treatment (e.g., dietary management, physical exercise)	Comparison of different GLP-1RAs individuals; comparison of different doses of one type of GLP-1RAs (e.g., dulaglutide 3.0mg vs. dulaglutide 1.5mg); comparison of different formulation of one type of GLP-1RAs (subcutaneous semaglutide vs. oral semaglutide); comparison of different frequency of one type of GLP-1RAs (e.g., exenatide BID vs. exenatide QW)
Outcomes	Primary outcome: gallbladder or biliary diseases; Secondary outcomes: the subcategories of gallbladder or biliary diseases.	No primary or secondary outcome data available, either effect estimate for compared groups or number/rate of events in each group.
Study design/Settings	Randomized controlled clinical trials (RCTs)	Reviews or non-RCTs; cross-over study designs; post hoc analyses of the same trial data; uncompleted or withdrawn studies

Note: GLP-1RAs: glucagon-like peptide 1 receptor agonists; RCTs, randomized controlled clinical trials.

eTable 2. Baseline characteristics of studies and participants included

Trials	No. of participants	Treatment duration	Population	Age (year)	No. (%) of female	BMI (kg/m^2)	Weight (kg)	HbA1c (%)	Interventions	Controls
Liraglutide										
LEAD-1 (2009)	1041	26 weeks	T2DM with OAD; BMI ≤ 45 kg/m^2	55.9	526 (50.5%)	29.9	81.6	8.4%	Liraglutide 0.6 mg; liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Placebo; rosiglitazone
LEAD-4 (2009)	510	26 weeks	T2DM with OAD; BMI ≤ 45 kg/m^2	55.0	289(56.7%)	33.5	-	8.5%	liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Placebo
Seino et. al. (2010)	400	24 weeks	T2DM; BMI < 35 kg/m^2	58.3	132 (33.0%)	24.5	65.0	8.9%	Liraglutide 0.9 mg, daily	Glibenclamide
LEAD-3 Mono (2011)	745	104 weeks	T2DM with oral monotherapy; BMI≤ 45 kg/m^2	53.0	375 (50.3%)	33.1	92.9	8.4%	Liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Glimepiride
1860-LIRA-DPP-4 (2011)	658	52 weeks	T2DM with metformin; BMI < 45 kg/m^2	55.9	316 (48.0%)	32.8	93.8	8.4%	Liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Sitagliptin
Astrup et. al. (2012)	466	104 weeks	BMI 30-40 kg/m^2; without T1DM or T2DM	45.9	355 (76.2%)	34.7	97.2	-	Liraglutide 1.2 mg; liraglutide 1.8 mg; liraglutide 2.4 mg; liraglutide 3.0 mg; daily	Orlistat
SCALE Maintenance (2013)	422	56 weeks	BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 if the patient had dyslipidemia or hypertension	46.2	344 (81.5%)	36.0	100.4	5.6%	Liraglutide 3.0 mg, daily	Placebo
SCALE Sleep Apnea (2013)	355	32 weeks	OSA; BMI > 30 kg/m^2	48.5	101 (28.1%)	38.1	-	-	Liraglutide 3.0 mg, daily	Placebo
SCALE Obesity and Prediabetes (2015) [a]	1444	56 weeks	BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 if the patient had dyslipidemia or hypertension; without prediabetes	41.5	1194 (82.7%)	37.4	103.8	5.3%	Liraglutide 3.0 mg, daily	Placebo
SCALE Diabetes	844	58 weeks	T2DM; overweight or obese (BMI > 27 kg/m^2)	54.9	421 (49.9%)	37.2	106.0	7.9%	Liraglutide 1.8 mg; liraglutide 3.0 mg; daily	Placebo

(2015)										
EAGLE study (2015)	965	24 weeks	T2DM; BMI > 25 kg/m^2	57.3	431 (44.7%)	31.9	90.5	9.1%	Liraglutide 1.8 mg, daily	Insulin glargine
LEADER (2016)	9360	3.8 years	T2DM with high risks of CVD	64.3	3337 (35.6%)	32.5	91.9	8.7%	Liraglutide 1.8 mg, daily	Placebo
LIRA-RENAL (2016)	277	26 weeks	T2DM with moderate renal impairments; BMI 25-45 kg/m^2	67.2	137 (49.5%)	33.5	94.6	8.1%	Liraglutide 1.8 mg, daily	Placebo
SCALE Obesity and Prediabetes (2017) [a]	2248	3 years	BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 if the patient had dyslipidemia or hypertension; with prediabetes	47.4	1714 (76.5%)	38.9	107.7	5.8%	Liraglutide 3.0 mg, daily	Placebo
Larsen et. al. (2017)	100	16 weeks	Schizophrenia spectrum disorder; prediabetes; BMI ≥ 27 kg/m^2	42.5	37 (38.1%)	33.8	102.8	5.6%	Liraglutide 1.8mg, daily	Placebo
LIPT study (2017)	72	26 weeks	Woman with PCOS and/or presence of IR; BMI>25 kg/m^2	28.8	72 (100%)	33.3	92.7	5.3%	Liraglutide 1.8 mg, daily	placebo
SCALE-IBT (2020)	282	56 weeks	BMI ≥ 30 kg/m^2	47.2	235 (83.3%)	39.0	107.6	5.5%	Liraglutide 3.0 mg + IBT, daily	Placebo + IBT
SCALE Insulin (2020)	392	56 weeks	T2DM; BMI > 27 kg/m^2	56.7	207 (52.3%)	35.6	99.7	7.9%	Liraglutide 3.0 mg + IBT + insulin, daily	Placebo + IBT + insulin
LIRA-ADD2SGLT2i (2020)	302	26 weeks	T2DM with SGLT-2i; BMI > 20 kg/m^2	55.2	120 (40%)	32.2	91.1	8.0%	Liraglutide 1.8 mg, daily	Placebo
Lundgren et.al. (2021)	195	1.0 year	BMI 32-43 kg/m^2	43.0	25 (63%)	32.6	96.7	5.3%	Liraglutide 3.0 mg, Liraglutide 3.0 mg + exercise; daily	Placebo; exercise
Subcutaneous semaglutide										
SUSTAIN-1 (2017)	387	30 weeks	T2DM treated with diet and exercise alone	53.7	177 (46%)	32.9	91.9	8.1%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Placebo
SUSTAIN-2	1225	56 weeks	T2DM with OAD	55.1	605 (49.4%)	32.5	89.5	8.1%	Semaglutide 0.5mg;	Sitagliptin

(2017)									semaglutide 1.0mg; weekly	
SUSTAIN-4 (2017)	1082	30 weeks	T2DM with metformin; insulin-naïve patients	56.5	508 (47%)	33.0	93.5	8.2%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Insulin glargine
SUSTAIN-6 (2017)	3297	104 weeks	T2DM with high risks of CVD	64.6	1295(39.3%)	32.8	92.1	8.7%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Placebo
SUSTAIN-5 (2018)	396	30 weeks	T2DM with basal insulin and/or metformin therapy	58.8	174 (43.9%)	32.2	91.7	8.4%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Placebo
Seino et. al. (2017)	308	30 weeks	T2DM with or without OAD monotherapy	58.3	73 (23.7%)	25.4	69.3	8.1%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Sitagliptin
M O'Neil et. al. (2018)	854	52 weeks	BMI ≥ 30 kg/mg^2 without diabetes	47.0	545 (64.3%)	39.3	111.5	5.5%	Semaglutide 0·05 mg, 0.1mg, 0.2mg, 0.3mg, 0.4mg; daily	Placebo
Kaku et. al. (2018)	600	56 weeks	T2DM with or without OAD monotherapy	58.5	171(0.285)	26.4	71.5	8.1%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Additional OAD
SUSTAIN-8 (2019)	786	52 weeks	T2DM with metformin treatments	56.6	364 (46%)	32.3	90.2	8.3%	Semaglutide 1.0mg; weekly	Canagliflozin
SUSTAIN-China (2021)	867	30 weeks	T2DM with metformin monotherapy	53.0	367 (42.6%)	27.8	76.4	8.1%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Sitagliptin
STEP-1 (2021)	1961	68 weeks	BMI ≥ 30 kg/mg^2 or BMI ≥ 27 kg/mg^2 with one or more coexisting conditions	46.5	1453 (74.1%)	37.9	105.3	5.7%	Semaglutide 2.4 mg; weekly	Placebo
STEP-2 (2021)	1210	68 weeks	T2DM; BMI ≥ 27 kg/mg^2; failed with dietary effort to lose weight	55.0	616 (50.9%)	35.7	99.8	8.1%	Semaglutide 1.0 mg; semaglutide 2.4 mg; weekly	Placebo
STEP-3 (2021)	611	68 weeks	BMI ≥ 30 kg/mg^2 or BMI ≥ 27 kg/mg^2 with one or more coexisting	46.0	495 (81.0%)	38.0	105.3	5.7%	Semaglutide 2.4 mg; weekly	Placebo

			conditions							
Newsome et. al. (2021)	319	72 weeks	NASH or NAFLD; BMI ≥ 25 kg/mg^2; with or without T2DM	55.0	194 (60.8%)	35.7	98.4	7.3%	Semaglutide 0.1 mg; Semaglutide 0.2 mg; Semaglutide 0.4 mg; daily	Placebo
Oral semaglutide										
Davies et. al. (2017)	421	26 weeks	T2DM with management only by diet and exercise or metformin; BMI 25-40 kg/m^2	57.2	214 (38.1%)	31.9	92.8	7.9%	Oral semaglutide 5 mg, 10mg, 20 mg, 40mg; daily	Placebo
PIONEER-1 (2019)	703	26 weeks	T2DM with management only by diet and exercise	55.0	346 (49.2%)	31.8	88.1	8.0%	Oral semaglutide 14 mg; daily	Placebo
PIONEER-2 (2019)	819	52 weeks	T2DM with metformin	58.0	406 (49.5%)	32.8	91.6	8.1**%**	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Empagliflozin
PIONEER-3 (2019)	1861	78 weeks	T2DM with metformin treatments; with or without sulfonylurea	58.0	879 (47.2%)	32.4	91.3	8.3%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Sitagliptin
PIONEER-4 (2019)	714	52 weeks	T2DM with metformin treatments	56.0	341 (48%)	33.0	94.0	8.0%	Oral semaglutide 14 mg; liraglutide 1.8mg; daily	Placebo
PIONEER-6 (2019)	3183	82 weeks	T2DM with high risks of CVD or CKD	66.0	1007 (31.6%)	32.3	90.9	8.2%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Placebo
PIONEER-7 (2019)	503	52 weeks	T2DM with other OAD	57.4	219 (43.5%)	31.5	88.6	8.3%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Sitagliptin
PIONEER-8 (2019)	730	52weeks	T2DM with insulin therapy	61.0	336 (46%)	31.0	85.9	8.2%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Placebo
Dulaglutide										
AWARD-1 (2014)	700	26 weeks	T2DM with OAD monotherapy; BMI 23-45 kg/m^2	56.0	406 (58.0%)	33.0	96	8.1%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Placebo
Ferdinand et. al. (2014)	755	26 weeks	T2DM with OAD treatments; BMI ≥ 23 kg/m^2	56.5	363 (48.1%)	33.0	-	7.9%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Placebo
AWARD-2	807	52 weeks	T2DM with OAD	56.6	393 (48.7%)	31.5	86.3	8.1%	Dulaglutide 0.75mg;	Insulin glargine

(2015)			treatments; BMI 23-45kg/m^2						dulaglutide 1.5mg; weekly	
AWARD-3 (2015)	807	26 weeks	T2DM with one OAD monotherapy or diet and exercise alone	56.7	454 (56.3%)	33.3	92.3	7.6%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Metformin
AWARD-4 (2015)	884	52 weeks	T2DM; BMI 23-45 kg/m^2	59.4	411 (46.5%)	32.5	91.2	8.4%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Insulin glargine
AWARD-5 (2015)	1098	104 weeks	T2DM with other OAD; BMI 25-40 kg/m^2	54.0	577 (52.5%)	31.0	86.5	8.1%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Sitagliptin; placebo
Araki et. al. (2015)	361	26 weeks	T2DM with sulphonylureas and/or metformin; BMI 18.5-35 kg/m^2	56.8	107 (29.0%)	26.0	71.0	8.0%	Dulaglutide 0.75mg; weekly	Insulin glargine
AWARD-7 (2018)	576	52 weeks	T2DM with moderate-to-severe renal impairments; with insulin treatments	64.5	275 (47.7%)	32.5	89.1	8.6%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Insulin glargine
AWARD-CHN1 (2018)	735	26 weeks	T2DM with OAD-naïve or OAD monotherapy; BMI 19-35 kg/m^2;	52.8	329 (45.7%)	26.2	-	8.0%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Glimepiride
AWARD-CHN2 (2018)	768	52weeks	T2DM with metformin and/or sulphonylurea; BMI 19-35 kg/m^2	55.0	338 (44.8%)	26.8	73.9	8.4%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Insulin glargine
REWIND (2019)	9892	7 years	T2DM with high risks of CVD or CKD; BMI≥23 kg/m^2	66.2	4589 (46.4%)	32.3	-	7.3%	Dulaglutide 1.5 mg; weekly	Placebo
Exenatide										
Heine et. al. (2005)	549	26 weeks	T2DM with inadequate glycemic control; BMI 25-45 kg/m^2	58.9	243 (44.2%)	31.4	87.9	8.2%	Exenatide 10 μg, twice daily	Insulin glargine
DURATION-2 (2010)	491	26 weeks	T2DM with metformin treatments; BMI 25-45 kg/m^2	52.3	237 (48.3%)	32.0	88.0	8.6%	Exenatide 2 mg, weekly	Pioglitazone; sitagliptin

Inagaki et. al. (2012)	427	52 weeks	T2DM with other OAD; BMI 18-35 kg/m^2	56.8	137 (32.1%)	26.2	70.5	8.5%	Exenatide 2 mg, weekly	Insulin glargine
EUREXA (2012)	1019	4.5 years	T2DM with metformin; BMI 25-40 kg/m^2	56.0	457 (46.4%)	32.	91.9	7.5%	Exenatide 10 µg, twice daily	Glimepiride
DURATION-3 (2014)	447	104 weeks	T2DM with metformin; BMI 25-45 kg/m^2	58.0	120 (52%)	32.5	91.2	8.3%	Exenatide 2 mg, weekly	Insulin glargine
Diamant et. al. (2014)	627	30 weeks	T2DM with other OAD; BMI ≥ 25 kg/m^2	59.5	134 (51.0%)	32.5	90.3	8.3%	Exenatide 10 µg + insulin glargine; twice daily	Insulin lispro + insulin glargine
Jaiswal et. al. (2015)	46	78 weeks	T2DM with mild-to-moderate DPN; with other OAD	53.0	20 (43.5%)	36.5	108.	8.3%	Exenatide 10 µg, twice daily	Insulin glargine
EXCEL (2017)	14737	7.5 years	T2DM with previous CVD	62.0	5603(38.0%)	31.8	-	8.0%	Exenatide 2 mg, weekly	Placebo
DURATION-8 (2020)	694	104 weeks	T2DM with inadequate glycemic control	54.3	357 (52.1%)	32.7	90.9	9.3%	Exenatide 2mg; exenatide 2mg + dapagliflozin; weekly	Dapagliflozin
Lixisenatide										
GETGOAL-Duo1 (2013)	446	24 weeks	T2DM with metformin and/or other OAD; BMI > 20 kg/m^2	56.0	224 (50%)	31.8	87.	7.6%	Lixisenatide 20 µg + insulin glargine + metformin, daily	Placebo + insulin glargine + metformin
GETGOAL-M (2013)	680	24 weeks	T2DM with metformin treatments	54.8	387 (56.9%)	32.9	90.1	8.1%	Lixisenatide 20 µg daily	Placebo
GETGOAL-P (2013)	484	24 weeks	T2DM with pioglitazone treatments	55.6	237 (60.0%)	34.0	94.8	8.1%	Lixisenatide 20 µg daily	Placebo
GETGOAL-F1 (2013)	483	24 weeks	T2DM with metformin monotherapy	56.1	266 (55.2%)	32.5	88.7	8.0%	Lixisenatide 20 µg daily	Placebo
GETGOAL-S (2014)	859	24 weeks	T2DM with sulphonylureas treatments	57.4	425 (49.5%)	30.3	83.6	8.2%	Lixisenatide 20 µg daily	Placebo
ELIXA (2015)	6063	225 weeks	T2DM with acute coronary events	59.8	1861(30.7%)	30.1	84.8	7.7%	Lixisenatide 20 µg daily	Placebo
Albiglutide										

HARMONEY-1 (2014)	301	52 weeks	T2DM with pioglitazone; BMI 20-45 kg/m^2 with or Without metformin	55.0	121 (40.2%)	34.1	98.9	8.1%	Albiglutide 30 mg + Pioglitazone; weekly	Placebo + pioglitazone
HARMONEY-3 (2014)	1012	104 weeks	T2DM with metformin; BMI 20-45 kg/m^2	54.8	530 (52.4%)	32.6	90.8	8.1%	Albiglutide 30-50 mg ; weekly	Placebo; sitagliptin; glimepiride
HARMONEY-4 (2014)	745	52 weeks	T2DM with metformin; BMI 20-45 kg/m^2	55.5	327 (43.9%)	33.1	94.9	8.3%	Albiglutide 30 mg + metformin; weekly	Insulin glargine+ metformin
Rosenstock et. al. (2014)	566	52 weeks	T2DM with insulin; BMI 20-45 kg/m^2	55.5	298 (52.6%)	-	92.1	8.4%	Albiglutide 30 mg+ insulin glargine; weekly	Lispro insulin + insulin glargine
Leiter et. al. (2014)	495	52 weeks	T2DM with renal impairments; BMI 20-45 kg/m^2	63.3	229 (46.3%)	30.4	80.0	8.2%	Albiglutide 30 mg, weekly	Sitagliptin
HARMONEY-5 (2015)	663	52 weeks	T2DM with metformin and sulphonylureas; BMI 20-45 kg/m^2	55.2	310 (46.8%)	32.2	90.8	8.2%	Albiglutide 30 mg, weekly	Placebo; pioglitazone
Harmony outcome (2018)	9432	1.5years	T2DM with established CVD	64.1	2894 (30.3%)	32.3	-	8.7%	Albiglutide 30-50 mg, weekly	Placebo
Rosenstock et. al. (2020)	813	26 weeks	T2DM with basal plus prandial insulin	58.0	442 (54.4%)	32.3	88.8	7.7%	Albiglutide 50 mg+ insulin glargine; weekly	Insulin lispro + insulin glargine

Notes: BMI, body mass index; T2DM, type 2 diabetes mellitus; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; T1DM, type 1 diabetes mellitus; CVD, cardiovascular diseases; CKD, chronic kidney disease; OAD, oral anti-diabetic drugs; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; PCOS: polycystic ovary syndrome.

[a] The SCALE Obesity and Prediabetes trial was divided into two groups (participants with or without prediabetes) because they had different follow-up periods.

eTable 3. Assessments of risks of bias of eligible studies according to Revised Cochrane risk-of-bias tool for randomized trials

Trials	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	No. of participants
LEAD-1(2009)[1]	some concerns	low	some concerns	low	low	1041
LEAD-4 (2009)[2]	low	low	low	low	some concerns	510
Seino et. al. (2010)[3]	low	low	low	low	some concerns	400
LEAD-3 Mon (2011)[4]	low	low	low	low	some concerns	745
1860-LIRA-DPP-4 (2011)[5]	low	some concerns	some concerns	low	some concerns	658
Astrup et. al. (2012)[6]	low	some concerns	some concerns	low	some concerns	466
SCALE Maintenance (2013)[7]	low	low	low	low	some concerns	422
SCALE Sleep Apnea (2013)[8]	low	low	some concerns	low	low	355
SCALE Obesity and Prediabetes (2015)[9]	low	low	some concerns	low	some concerns	1444
SCALE Diabetes (2015)[10]	low	low	low	low	low	844
EAGLE study (2015)[11]	low	some concerns	low	low	low	965
LEADER (2016)[12]	low	low	low	low	low	9360
LIRA-RENAL (2016)[13]	low	low	low	low	some concerns	277
SCALE Obesity and Prediabetes (2017)[14]	low	low	low	low	low	2248
Larsen et. al. (2017)[15]	low	low	low	low	low	100
LIPT (2017)[16]	low	low	low	low	low	72
SCALE-IBT (2020)[17]	low	low	low	low	low	282
SCALE Insulin (2020)[18]	low	low	low	low	low	392
LIRA-ADD2SGLT2i (2020)[19]	low	low	low	low	low	302
Lundgren et.al. (2021)[20]	low	low	low	low	low	195
SUSTAIN-1(2017)[21]	low	low	low	low	low	387
SUSTAIN-2(2017)[22]	low	low	low	low	low	1225
SUSTAIN-4(2017)[23]	low	low	low	low	low	1082
SUSTAIN-6(2017)[24]	low	low	low	low	low	3297
Seino et. al. (2017)[25]	low	some concerns	low	low	some concerns	308
SUSTAIN-5 (2018)[26]	low	low	low	low	low	396
M O'Neil et. al. (2018)[27]	some concerns	low	some concerns	low	low	854
Kaku et. al. (2018)[28]	low	some concerns	low	low	low	600
SUSTAIN-8 (2019)[29]	low	low	low	low	some concerns	786
SUSTAIN China (2021)[30]	low	low	low	low	some concerns	867
STEP-1(2021)[31]	low	low	low	low	low	1961
STEP-2(2021)[32]	low	low	low	low	low	1207

STEP-3(2021)[33]	low	low	low	low	low	611
Newsome et. al. (2021)[34]	low	low	low	low	low	319
Davies et. al. (2017)[35]	low	some concerns	low	low	Some concerns	421
PIONEER-1(2019)[36]	low	low	low	low	some concerns	703
PIONEER-2(2019)[37]	low	some concerns	low	low	some concerns	819
PIONEER-3 (2019)[38]	low	low	low	Some concerns	some concerns	1861
PIONEER-4 (2019)[39]	low	low	low	low	some concerns	714
PIONEER-6 (2019)[40]	low	low	low	low	low	3183
PIONEER-7 (2019)[41]	low	low	low	low	some concerns	503
PIONEER-8 (2019)[42]	low	low	low	low	some concerns	730
AWARD-1 (2014)[43]	some concerns	low	low	low	some concerns	700
Ferdinand et. al. (2014)[44]	low	low	low	low	some concerns	755
AWARD-2 (2015)[45]	low	some concerns	low	low	some concerns	807
AWARD-3 (2015)[46]	low	low	low	low	some concerns	807
AWARD-4 (2015)[47]	low	low	low	low	some concerns	884
AWARD-5 (2015)[48]	low	low	some concerns	low	some concerns	1098
Araki et. al. (2015)[49]	low	some concerns	low	low	low	361
AWARD-7 (2018)[50]	low	low	low	low	some concerns	576
AWARD-CHN1(2018)[51]	low	low	low	low	low	735
AWARD-CHN2 (2018)[52]	low	some concerns	low	low	some concerns	768
REWIND (2019)[53]	low	low	low	low	low	9892
Heine et. al. (2005)[54]	low	some concerns	low	low	some concerns	549
DURATION-2 (2010)[55]	low	low	low	low	some concerns	491
EUREXA (2012)[56]	low	low	some concerns	low	some concerns	1019
Inagaki et. al. (2012)[57]	low	some concerns	low	low	low	427
DURATION-3 (2014)[58]	low	low	some concerns	low	Some concerns	447
Diamant et. al. (2014)[59]	low	low	some concerns	low	low	627
Jaiswal et. al. (2015)[60]	low	some concerns	low	low	low	46
DURATION-8 (2016)[61]	some concerns	low	some concerns	low	some concerns	694
EXCEL (2017)[62]	low	low	low	low	low	14737
GETGOAL-Duo1 (2013)[63]	low	low	low	low	some concerns	446

GETGOAL -M (2013)[64]	low	some concerns	low	low	some concerns	680
GETGOAL-S (2013)[65]	low	low	low	low	some concerns	859
GETGOAL-P (2013)[66]	low	some concerns	low	low	some concerns	484
GETGOAL-F1 (2013)[67]	low	low	low	low	some concerns	483
ELIXA (2015)[68]	low	low	low	low	low	6063
HARMONEY-1(2014)[69]	low	low	low	low	some concerns	301
HARMONEY-3 (2014)[70]	low	low	some concerns	low	some concerns	1012
HARMONEY-4 (2014)[71]	low	low	low	low	some concerns	745
Rosenstock et. al. (2014)[72]	low	some concerns	low	low	some concerns	566
Leiter et. al. (2014)[73]	low	some concerns	some concerns	low	some concerns	495
HARMONEY-5 (2015)[74]	low	low	low	low	Some concerns	663
Harmony outcome (2018)[75]	low	low	low	low	low	9432
Rosenstock et. al. (2020)[76]	low	low	low	low	some concerns	813

Notes: Domain 1: Risk of bias arising from the randomization process. Domain 2: Risk of bias due to deviations from the intended interventions. Domain 3: Risk of bias due to missing outcome data. Domain 4: Risk of bias in measurement of the outcome. Domain 5: Risk of bias in selection of the reported results.

eTable 4. GRADE summary of findings for each outcome in the meta-analysis

Outcomes	No. of patients (studies)	Study event rates		Relative effects (95% CI)	Anticipated absolute effect [a]		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of evidence
		Experiments	Controls		Risk with controls	Risk with GLP-1RAs						
Gallbladder or biliary diseases	103,371 (76 [b])	1.58% (916/57,856)	1.19% (544/45,515)	RR 1.37 (1.23, 1.52)	70 per 10,000	96 per 10,000 (86 to 107)	Not serious	Not serious	Not serious	Not serious	Not serious	High ⊕⊕⊕⊕
cholelithiasis	95,886 (61 [b])	0.85% (454/53,674)	0.68% (287/42,212)	RR 1.27 (1.10, 1.47)	46 per 10,000	58 per 10,000 (51 to 67)	Not serious	Not serious	Not serious	Not serious	Not serious	High ⊕⊕⊕⊕
cholecystitis	90,137 (53 [b])	0.61% (302/49,491)	0.46% (187/40,574)	RR 1.36 (1.14, 1.62)	27 per 10,000	37 per 10,000 (31 to 41)	Not serious	Not serious	Not serious	Not serious	Not serious	High ⊕⊕⊕⊕
Biliary diseases	68,966 (21 [b])	0.21% (77/36,225)	0.13% (41/32,741)	RR 1.55 (1.08, 2.22)	9 per 10,000	14 per 10,000 (10 to 20)	Not serious	Not serious	Not serious	Not serious	Not serious	Moderate ⊕⊕⊕◯ [c]

Notes: GRADE, grading of recommendations assessment, development, and evaluation. GLP-1RAs, glucagon-like peptide 1 receptor agonists; T2DM, type 2 diabetes mellitus; RR, relative risk; CI, confidence intervals.

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] There were a total of 76 trials including 77 sets of data for gallbladder or biliary diseases, 61 trials including 62 sets of data for cholelithiasis, 53 trials for cholecystitis, and 21 trials for biliary diseases.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[c] Concerns about selective reporting.

eTable 5. Effects of factors on the risks of gallbladder or biliary diseases with GLP-1RAs in trials with diabetes treatment

Risk factors	No. of patients	No. of trials	Relative risks (95%CI)	Heterogeneity		*P*-value for interaction [a]
				I^2	*P*-value	
Dose of treatments [b]						0.08
High dose [c]	50,922	37	1.41 (1.21, 1.64)	0%	0.99	
Low dose [d]	15,913	29	1.04 (0.77, 1.42)	0%	0.62	
Duration of treatments						0.07
≤ 26 weeks	13,229	22	0.78 (0.46, 1.33)	0%	0.96	
> 26 weeks	78,817	39	1.29 (1.15, 1.45)	0%	0.77	
Baseline BMI [e]						0.14
High	73,830	42	1.23 (1.10, 1.39)	0%	0.80	
Low	17,203	17	1.69 (1.13, 2.53)	0%	0.90	
Control types						0.20
Placebo	68,506	29	1.30 (1.15, 1.47)	0%	0.92	
Active comparators	24,967	35	1.02 (0.73, 1.44)	0%	0.92	
Types of trials						0.16
CVOT	55,964	7	1.31 (1.16, 1.48)	22%	0.26	
Non-CVOT	35,635	53	1.05 (0.79, 1.40)	0%	0.98	

Note: GLP-1RAs, glucagon-like peptide 1 receptor agonists; CI, confidential intervals; T2DM, type 2 diabetes mellitus; CVOT, cardiovascular outcomes trials; BMI, body mass index.

[a] P-value for interaction is used to test groups difference.

[b] One trial might have two or more different dose of GLP-1RAs treatments. Among the studies included, only studies with liraglutide, subcutaneous semaglutide, oral semaglutide dulaglutide, and albiglutide had different dose of treatments. Lixisenatide and exenatide with single dose in eligible studies were not included to access the dosage-dependent effects.

[c] In trials with GLP-1RAs treatment for diabetes, the high dose groups included liraglutide ≥1.8 mg once-daily, subcutaneous semaglutide ≥ 1.0 mg once-weekly, oral semaglutide ≥7 mg once-daily, dulaglutide ≥ 1.5 mg once-weekly, and albiglutide ≥ 50 mg once-weekly.

[d] In trials with GLP-1RAs treatment for diabetes, low dose of GLP-1RAs included liraglutide 0.6-1.2 mg (< 1.8 mg) daily, subcutaneous semaglutide 0.5 mg (< 1.0 mg) once-weekly, oral semglutide 3.0 mg (< 7.0 mg) once-daily, dulaglutide 0.75 mg (< 1.5 mg) once-weekly, and albiglutide 30 mg (< 50 mg) once-weekly.

[e] The cut-off point of the baseline BMI was 31.6 kg/m^2 which was the mean of baseline BMI in trials using GLP-1RAs for diabetes.

eTable 6. Effects of factors on the risks of gallbladder or biliary diseases with GLP-1RAs in trials with treatment for weight loss

Risk factors	No. of patients	No. of trials	Relative risks (95%CI)	Heterogeneity		*P*-value for interaction [a]
				I^2	*P*-value	
Baseline BMI [b]						0.56
High	8,599	8	2.37 (1.66, 3.39)	0%	0.65	
Low	2,682	5	1.79 (0.76, 4.24)	0%	0.79	
Control types						0.59
Placebo	11,284	13	2.33 (1.67, 3.24)	0%	0.86	
Active comparators	466	1	1.28 (0.15, 10.83)	-	-	

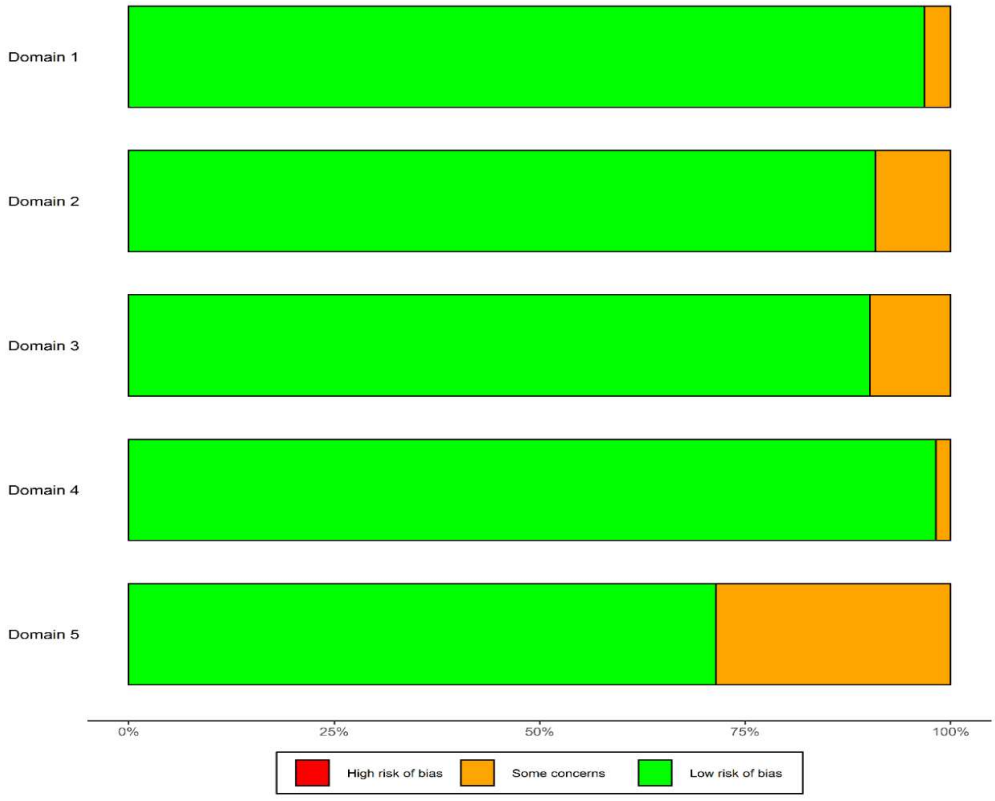
Note: GLP-1RAs, glucagon-like peptide 1 receptor agonists; CI, confidential intervals; BMI, body mass index.

[a] P-value for interaction is used to test groups difference.

[b] The cut-off point of the baseline BMI was 36.7 kg/m^2 which was the mean of baseline BMI in trials using GLP-1RAs for weight loss.

eFigure 1. Summary of risks of bias of all included studies

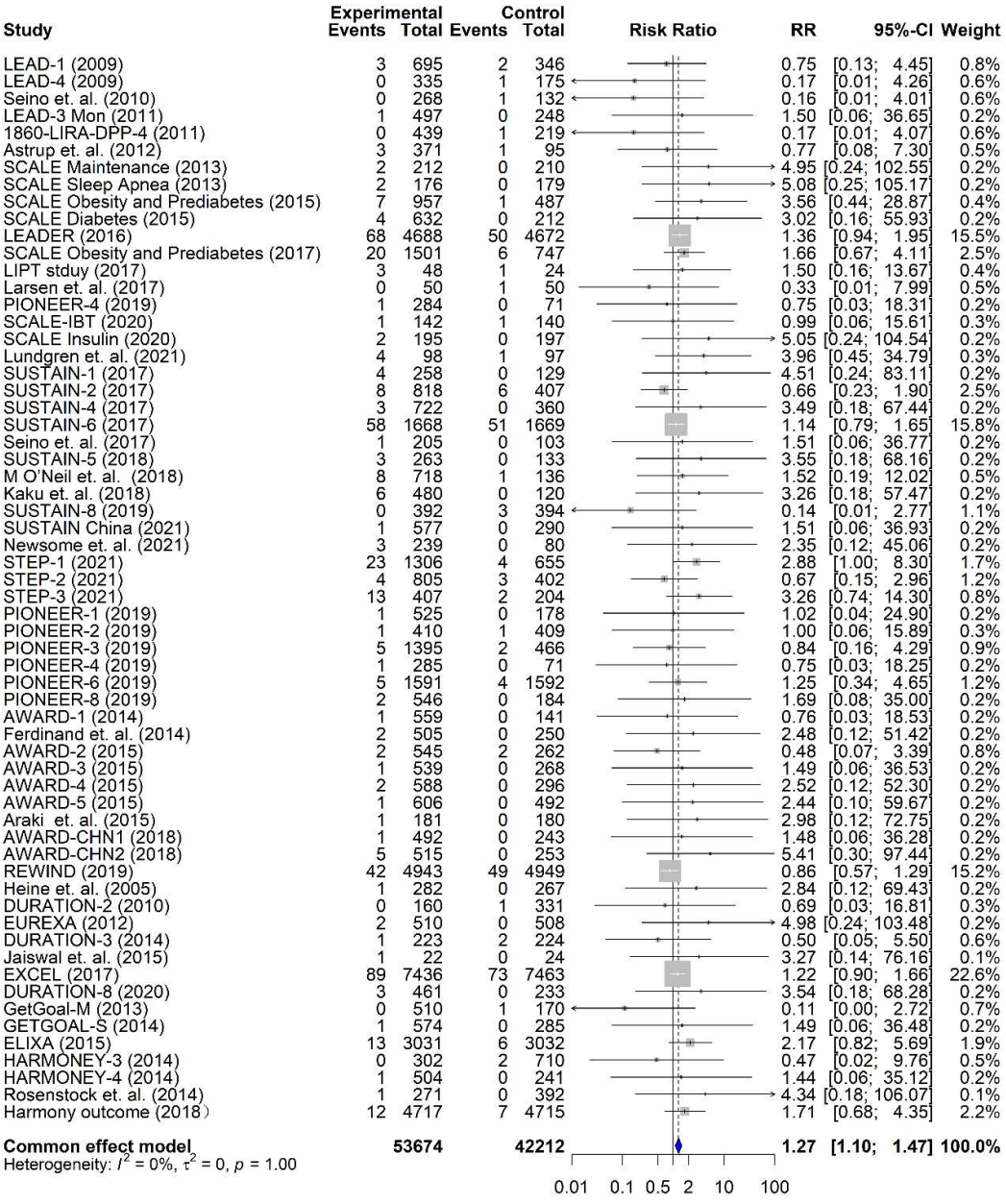
Notes: Domain 1: Risk of bias arising from randomization process Domain 2: Risk of bias due to deviations from intended interventions Domain 3: Risk of bias due to missing outcome data. Domain 4: Risk of bias in outcome measurements. Domain 5: Risk of bias in the selection of reported results.



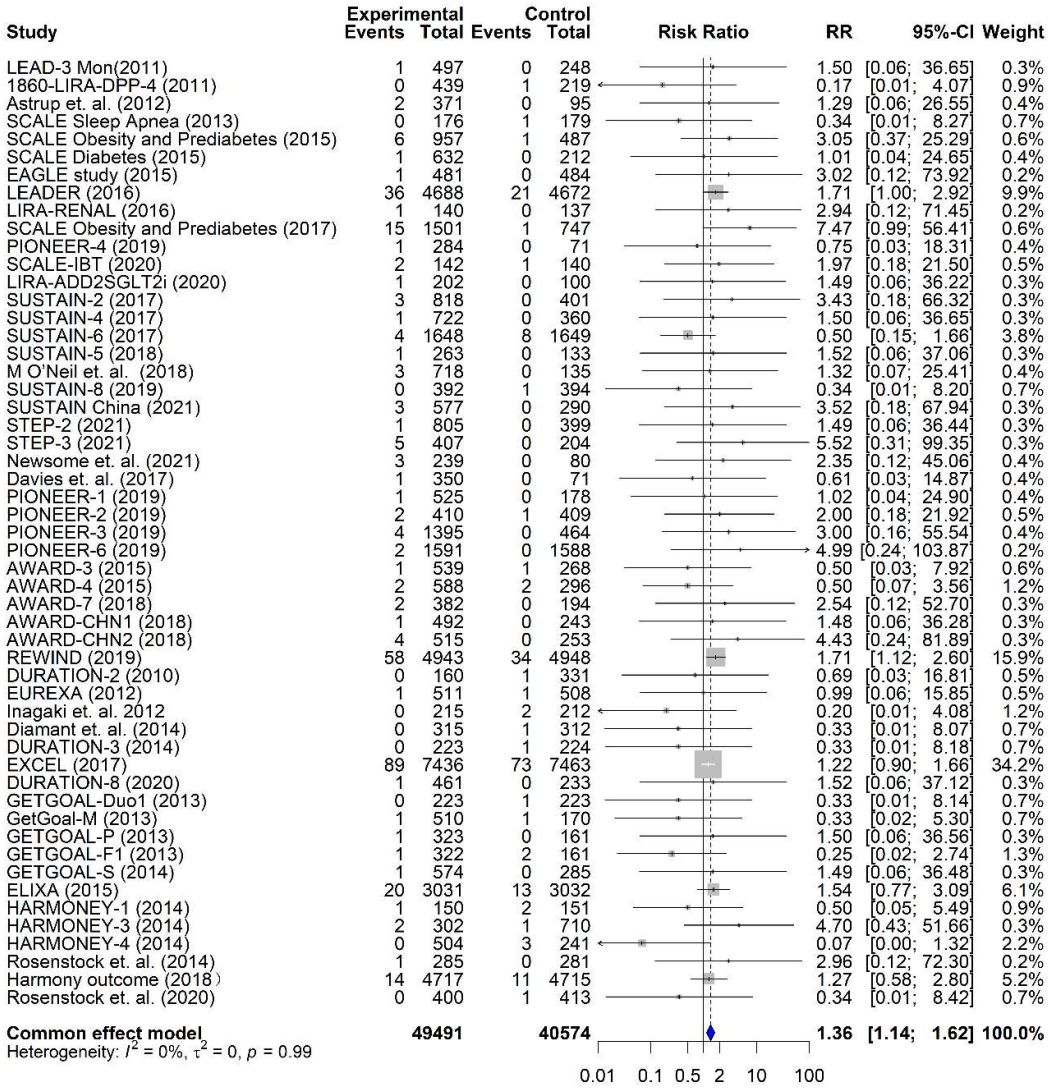
eFigure 2. Risks of cholelithiasis, cholecystitis, and biliary diseases in patients with GLP-1RAs treatments compared with controls

Notes: A, risks of cholelithiasis; B, risks of cholecystitis; C, risks of biliary diseases. Experimental, GLP-1RAs treatments; Control, placebo or active control. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

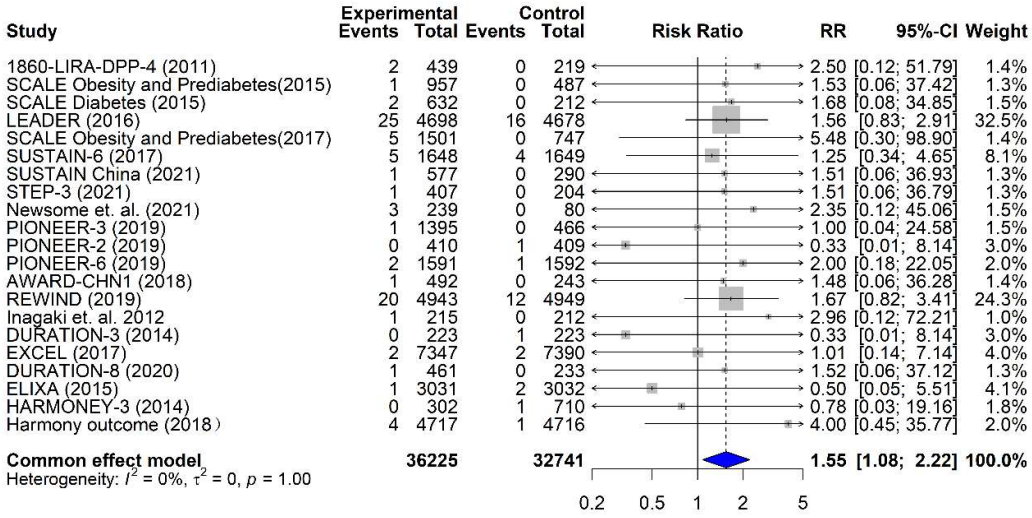
eFigure 2A. Risks of cholelithiasis in patients with GLP-1RAs



eFigure 2B. Risks of cholecystitis in patients with GLP-1RAs



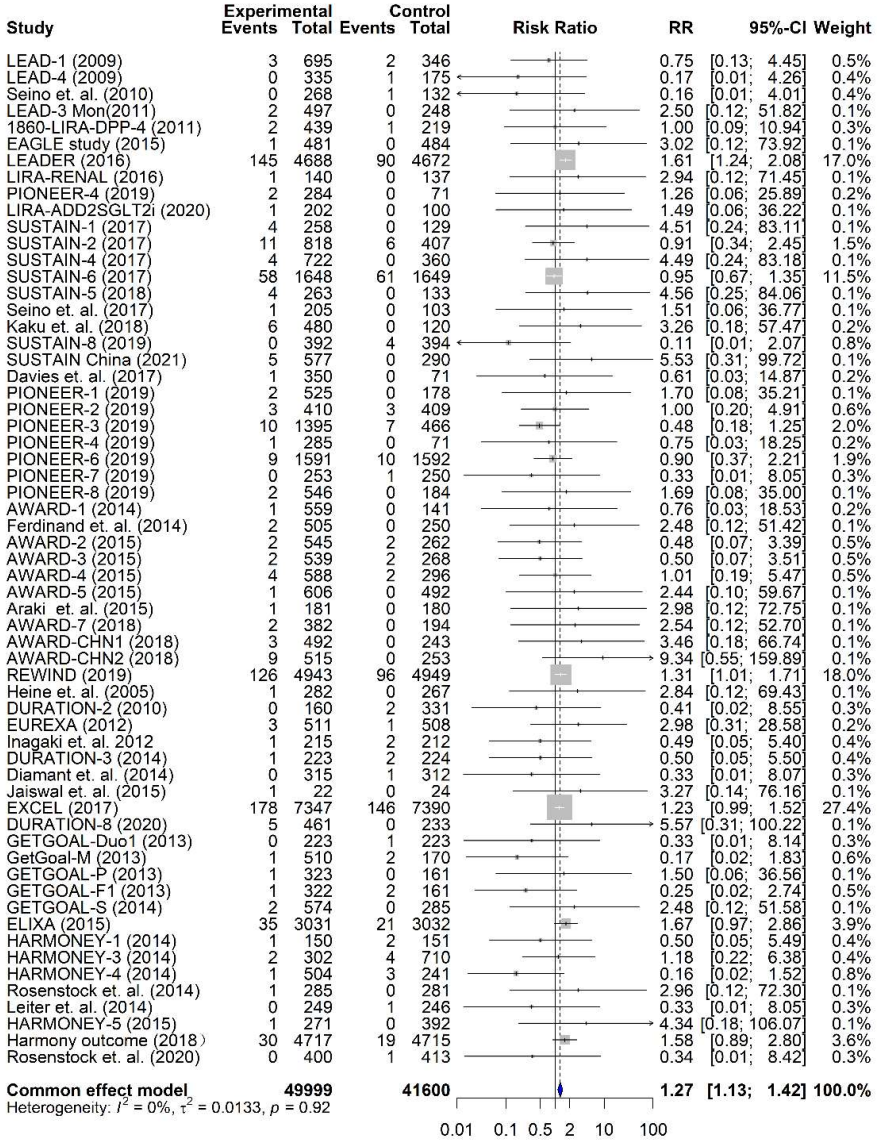
eFigure 2C. Risks of biliary diseases in patients with GLP-1RAs



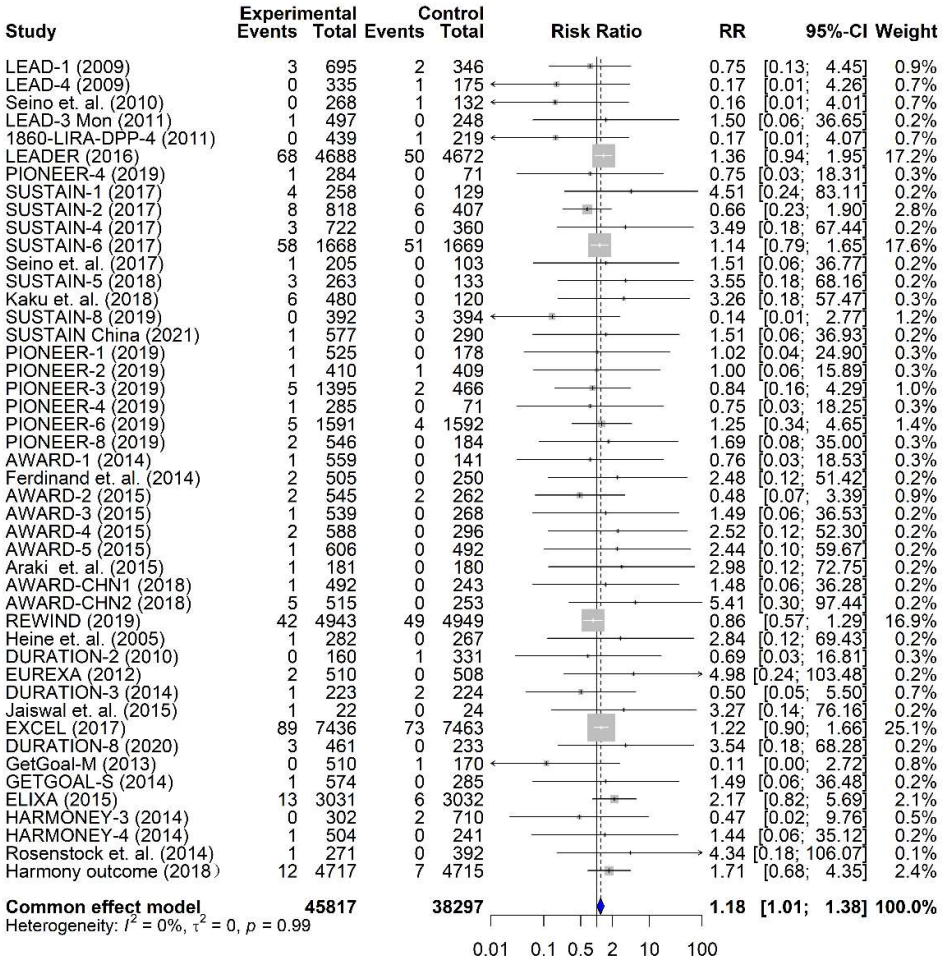
eFigure 3. Risks of the composite of gallbladder or biliary diseases, cholelithiasis, cholecystitis, and biliary diseases with GLP-1RAs compared with controls in trials in trials with treatment for diabetes

Notes: A, risks of cholelithiasis; B, risks of cholecystitis; C, risks of biliary diseases. Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

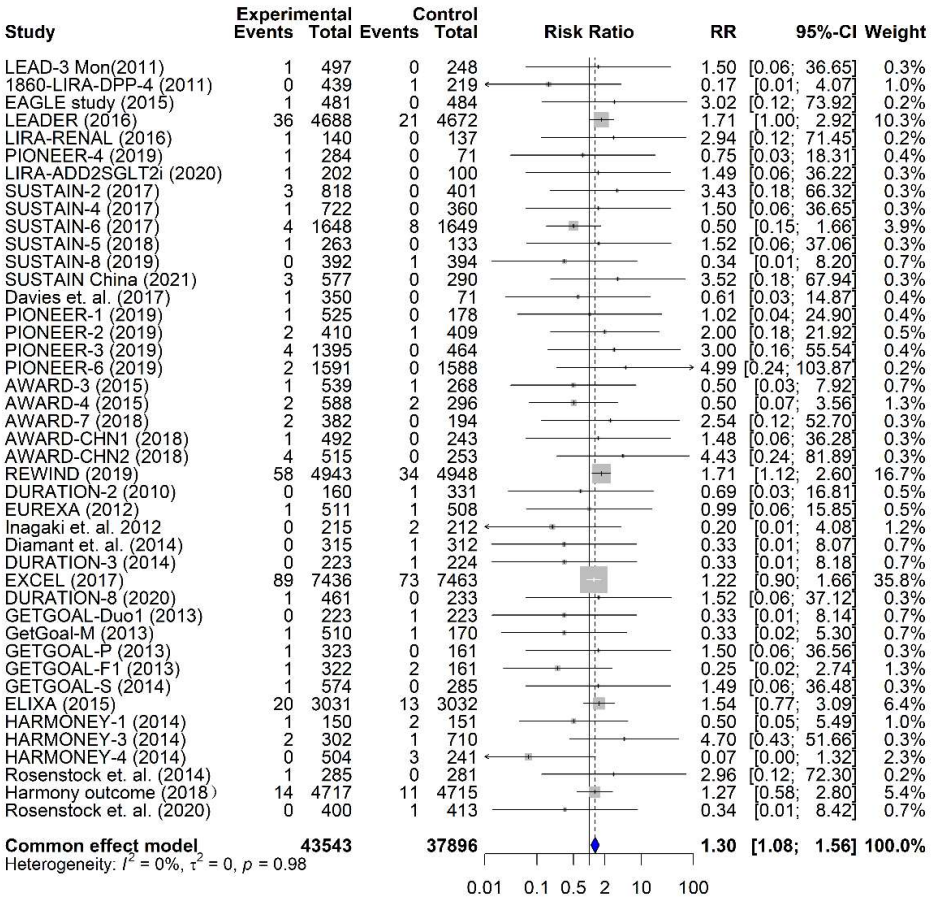
eFigure 3A. Risks of the composite of gallbladder or biliary diseases in patients with GLP-1RAs in trials with treatment for diabetes



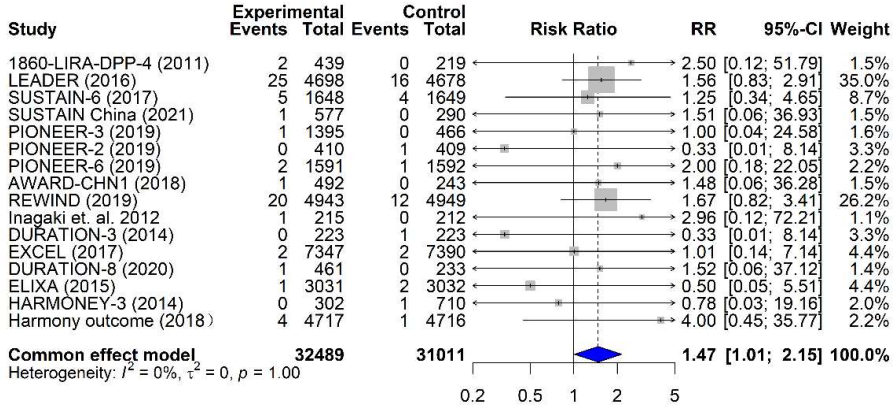
eFigure 3B. Risks of cholelithiasis in patients with GLP-1RAs in trials with treatment for diabetes



eFigure 3C. Risks of cholecystitis in patients with GLP-1RAs in trials with treatment for diabetes

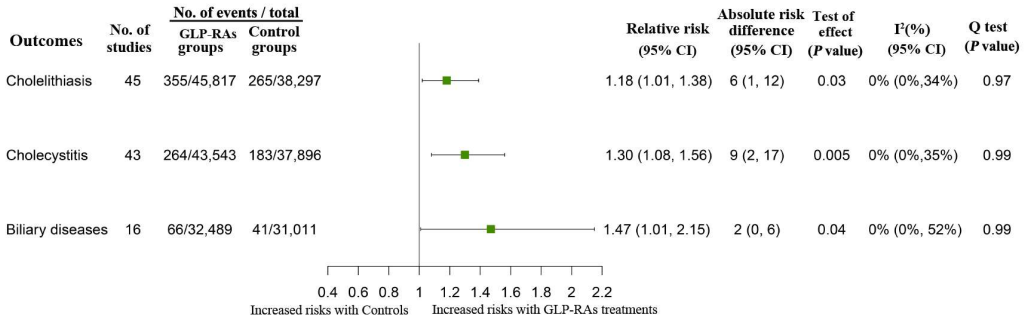


eFigure 3D. Risks of biliary diseases in patients with GLP-1RAs in trials with treatment for diabetes



eFigure 4. Overall risks of cholelithiasis, cholecystitis, and biliary diseases in patients with GLP-1RAs compared with controls in trials with treatment for diabetes

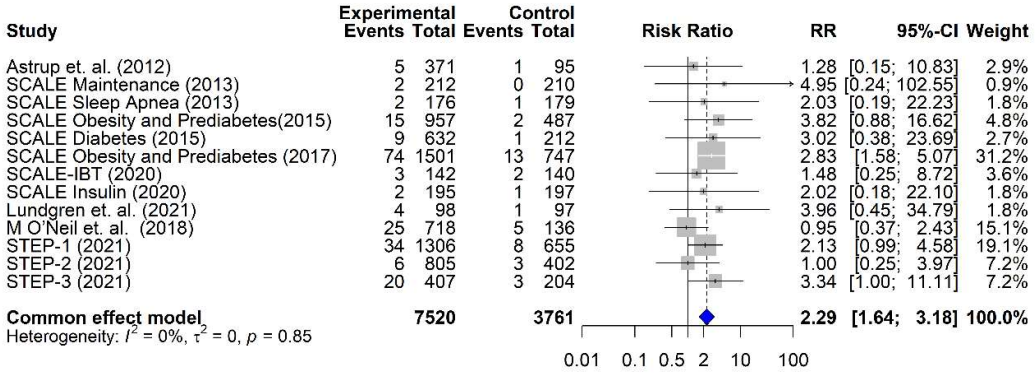
Notes: GLP-1RAs, glucagon-like peptide 1 receptor agonists; CI, confidence interval. Absolute risk difference is the number of events per 10,000 people in a year.



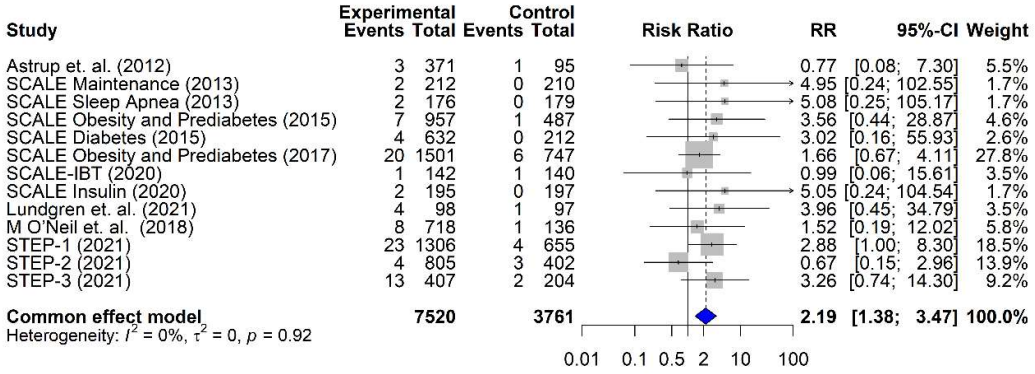
eFigure 5. Risks of the composite of gallbladder or biliary diseases, cholelithiasis, cholecystitis, and biliary diseases with GLP-1RAs compared with controls in trials with treatment for weight loss

Notes: A, risks of cholelithiasis; B, risks of cholecystitis; C, risks of biliary diseases. Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviation:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

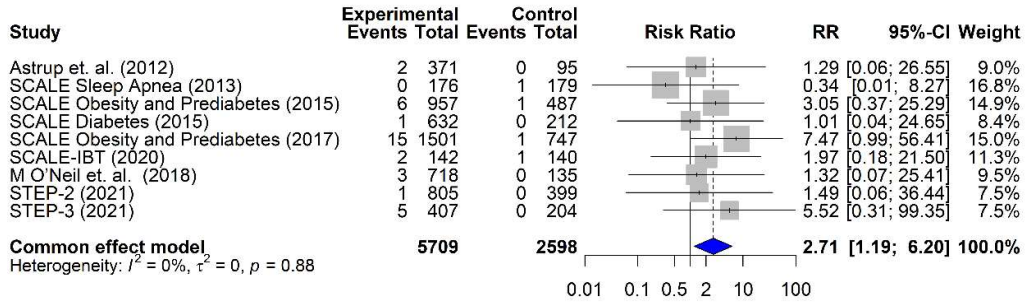
eFigure 5A. Risks of the composite of gallbladder or biliary diseases in patients with GLP-1RAs in trials with treatment for weight loss



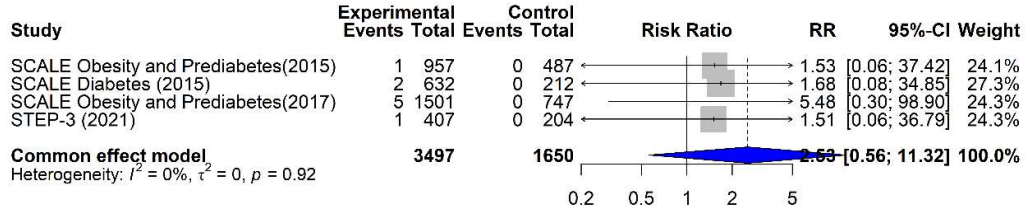
eFigure 5B. Risks of cholelithiasis in patients with GLP-1RAs in trials with treatment for weight loss



eFigure 5C. Risks of cholecystitis in patients with GLP-1RAs in trials with treatment for weight loss

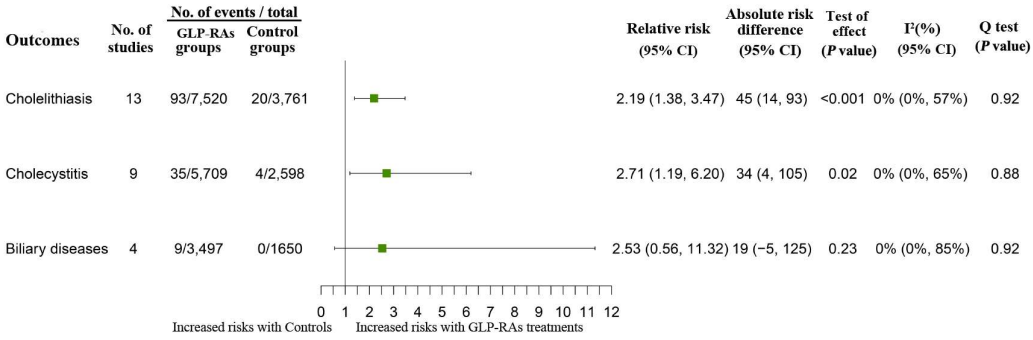


eFigure 5D. Risks of biliary diseases in patients with GLP-1RAs in trials with treatment for weight loss



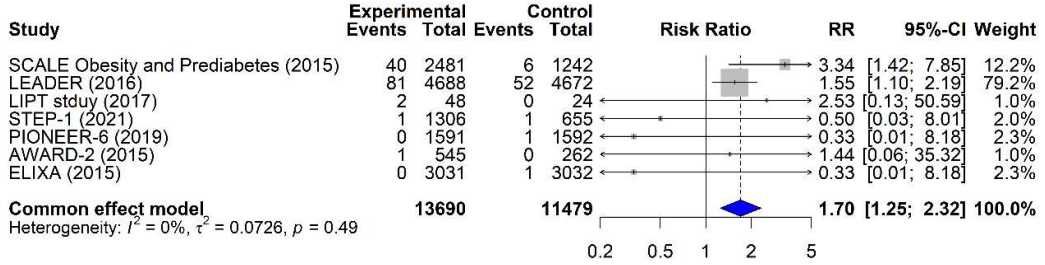
eFigure 6. Overall risks of cholelithiasis, cholecystitis and biliary diseases in patients with GLP-1RAs compared with controls in trials with treatment for weight loss

Notes: GLP-1RAs, glucagon-like peptide 1 receptor agonists; CI, confidence interval. Absolute risk difference is the number of events per 10,000 people in a year.



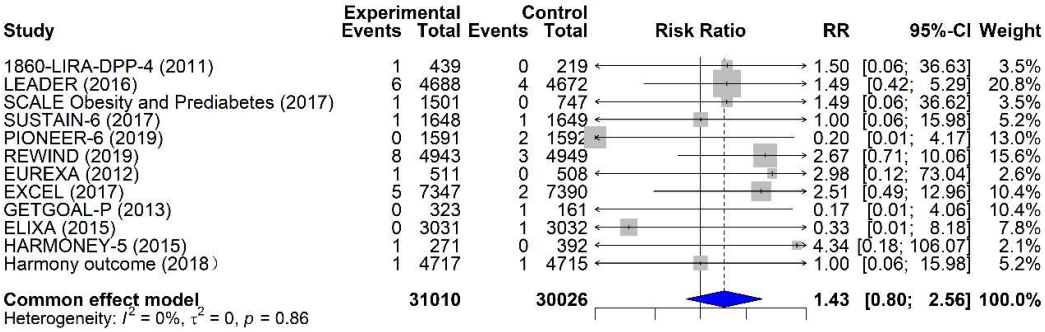
eFigure 7. Risks of cholecystectomy in patients with GLP-1RAs compared with controls

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.



eFigure 8. Risks of biliary tract cancer in patients with GLP-1RAs compared with controls

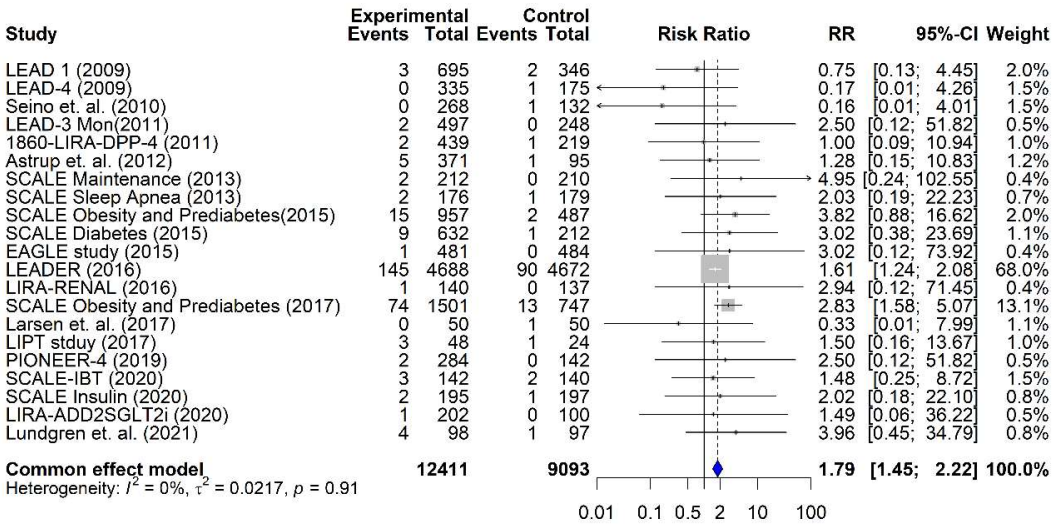
Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.



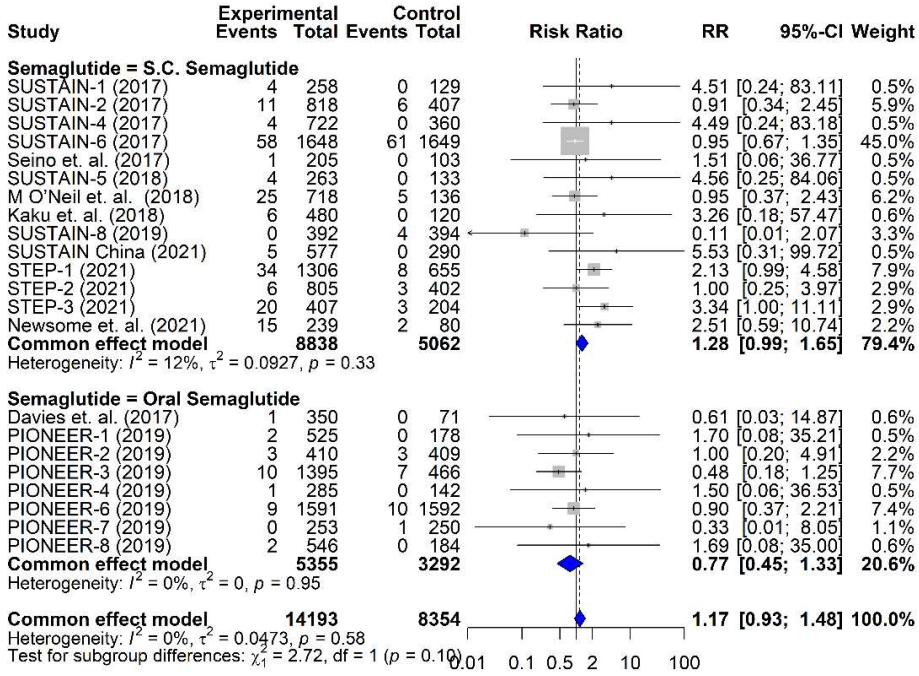
eFigure 9. Risks of gallbladder or biliary diseases in patients with different GLP-1RAs individuals compared with controls

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. The differences between individual GLP-1RAs were not significant (***P*-for interaction =0.07**). **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

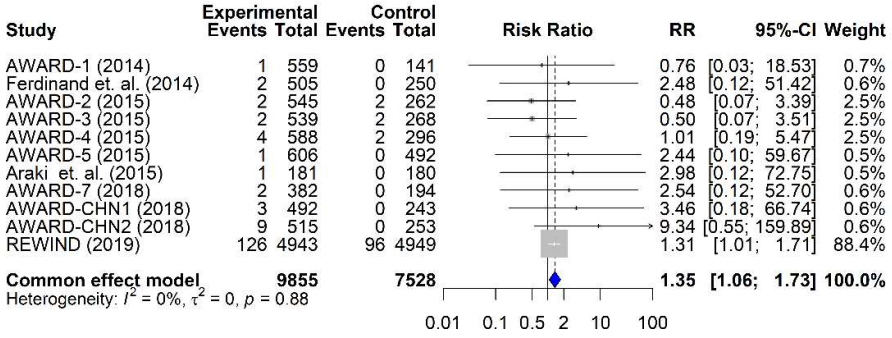
eFigure 9A. Association between gallbladder or biliary diseases and liraglutide



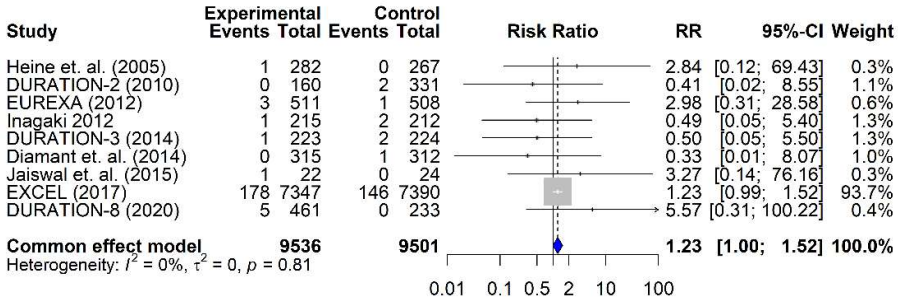
eFigure 9B. Association between gallbladder or biliary diseases and semaglutide



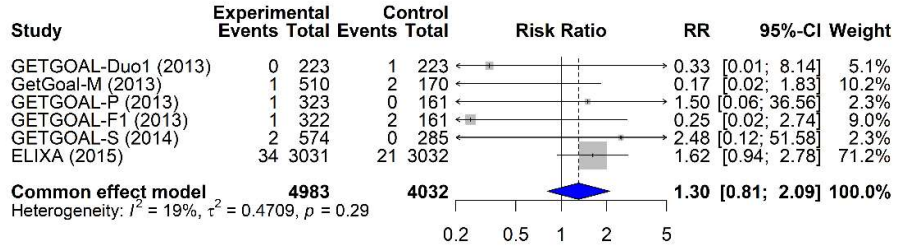
eFigure 9C. Association between gallbladder or biliary diseases and dulaglutide



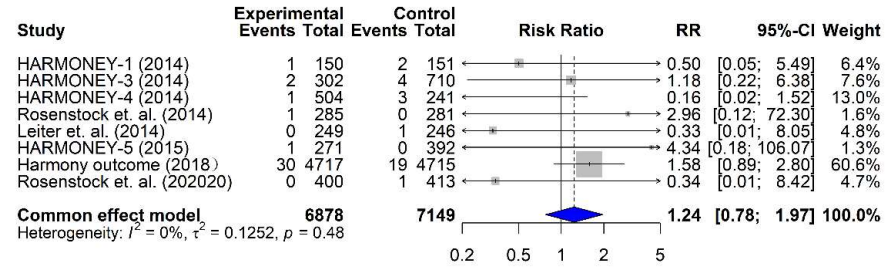
eFigure 9D. Association between gallbladder or biliary diseases and exenatide



eFigure 9E. Association between gallbladder or biliary diseases and lixisenatide

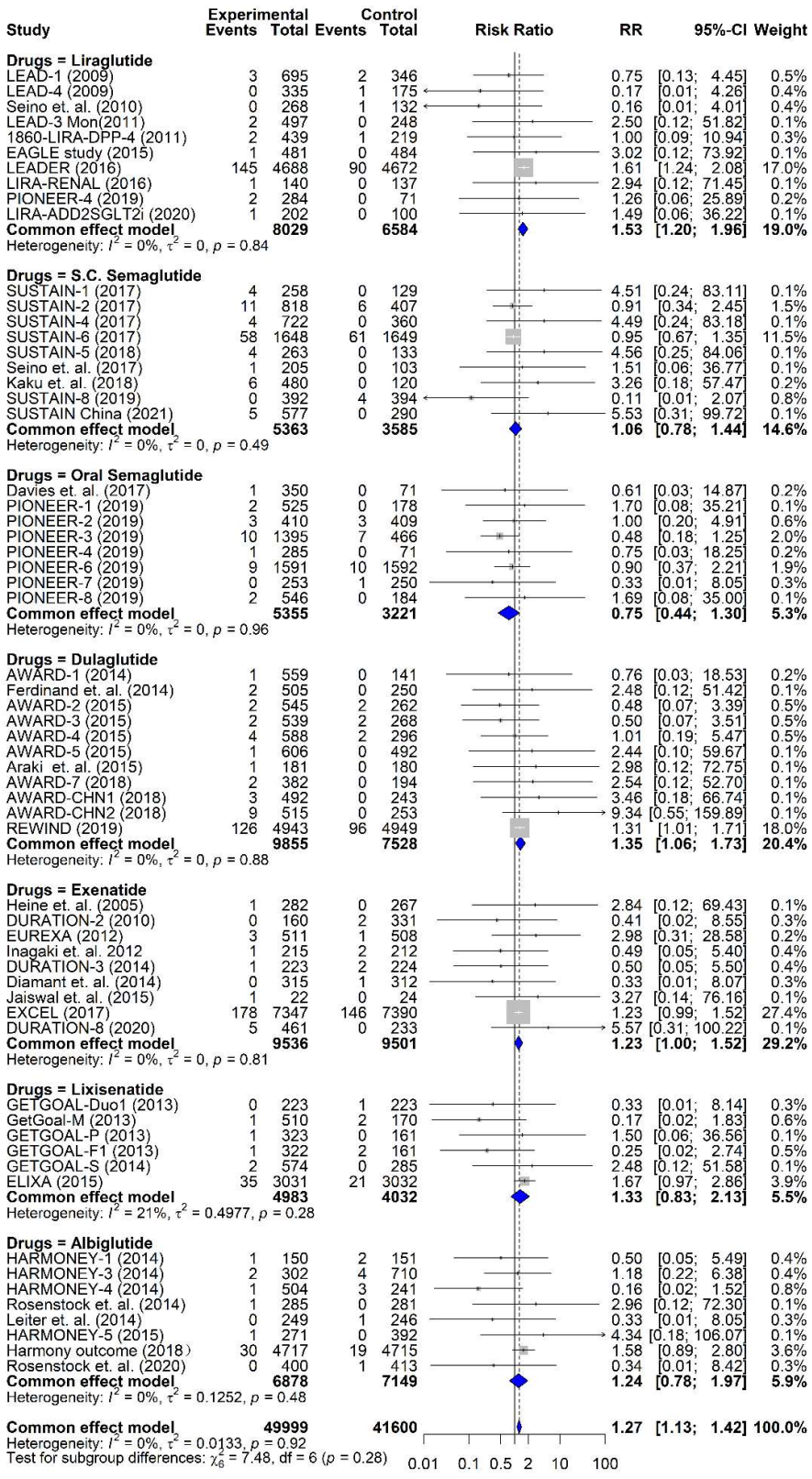


eFigure 9F. Association between gallbladder or biliary diseases and albiglutide



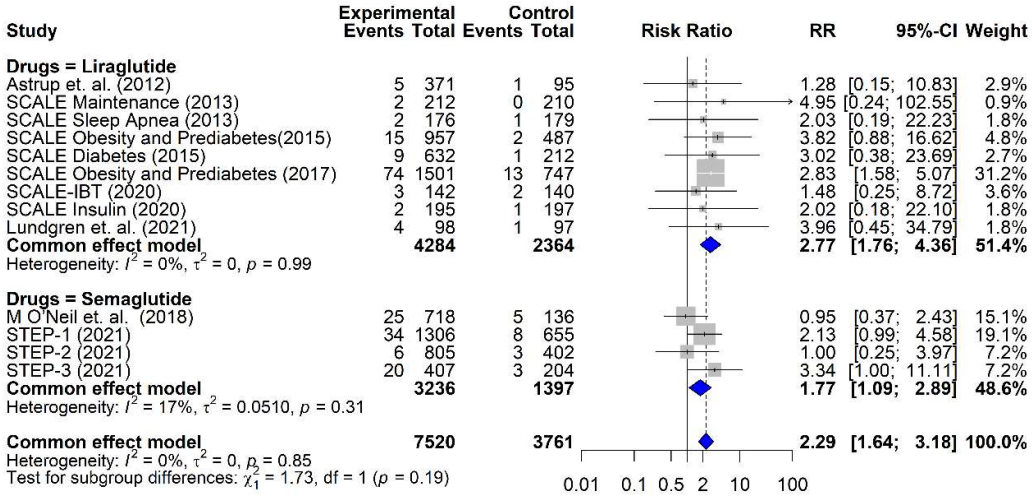
eFigure 10. Risks of gallbladder or biliary diseases with different GLP-1RAs medications compared with controls in trials with treatment for diabetes

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. Test for subgroup difference: The p values for interaction is 0.30. **Abbreviations:** RR, relative risks; CI, confidential intervals; GLP-1RAs, glucagon-like peptide 1 receptor agonists.



eFigure 11. Risks of gallbladder or biliary diseases with different GLP-1RAs medications compared with controls in trials for weight loss

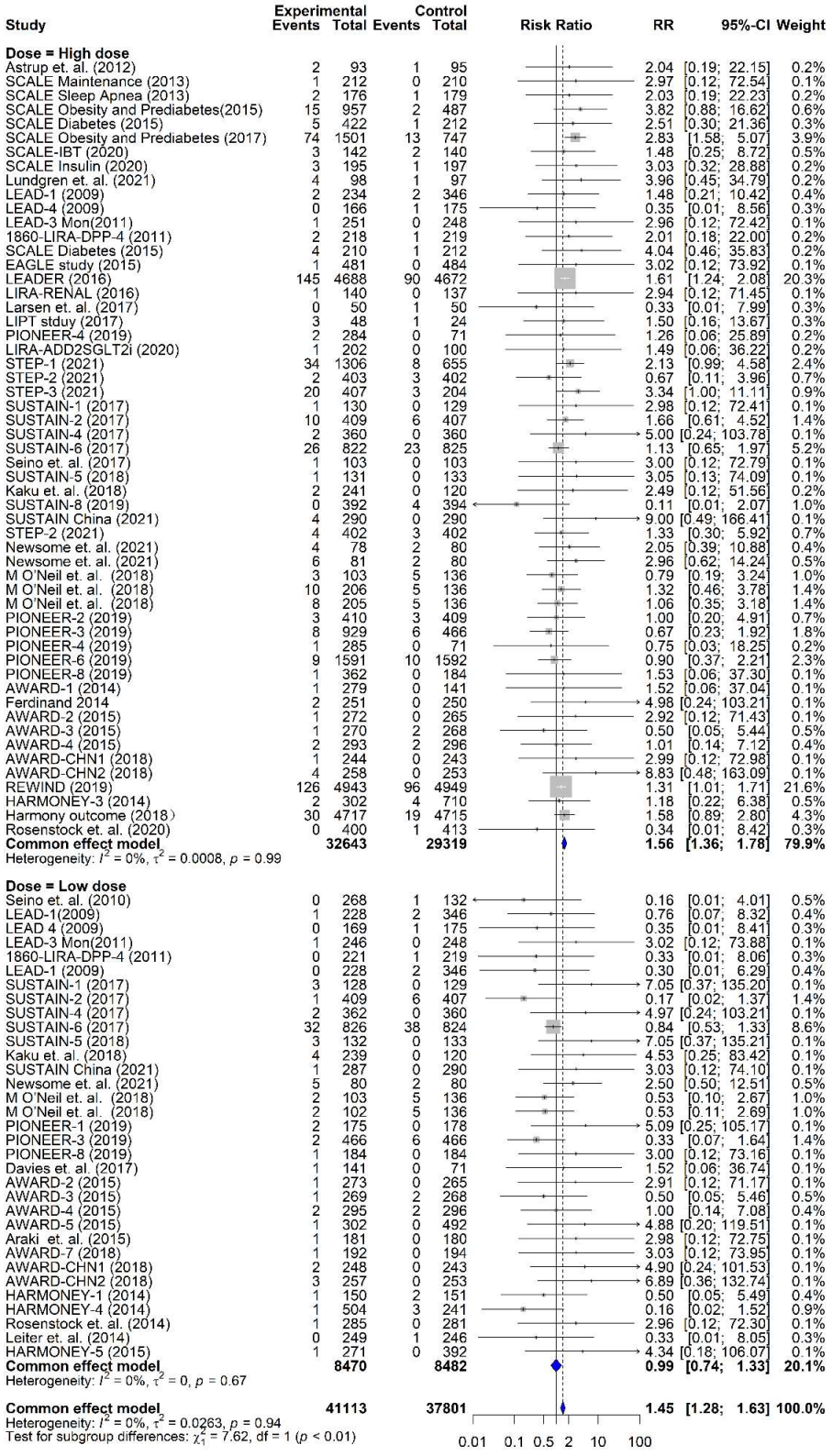
Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. Test for subgroup difference: The p values for interaction is 0.19. **Abbreviations:** RR, relative risks; CI, confidential intervals; GLP-1RAs, glucagon-like peptide 1 receptor agonists.



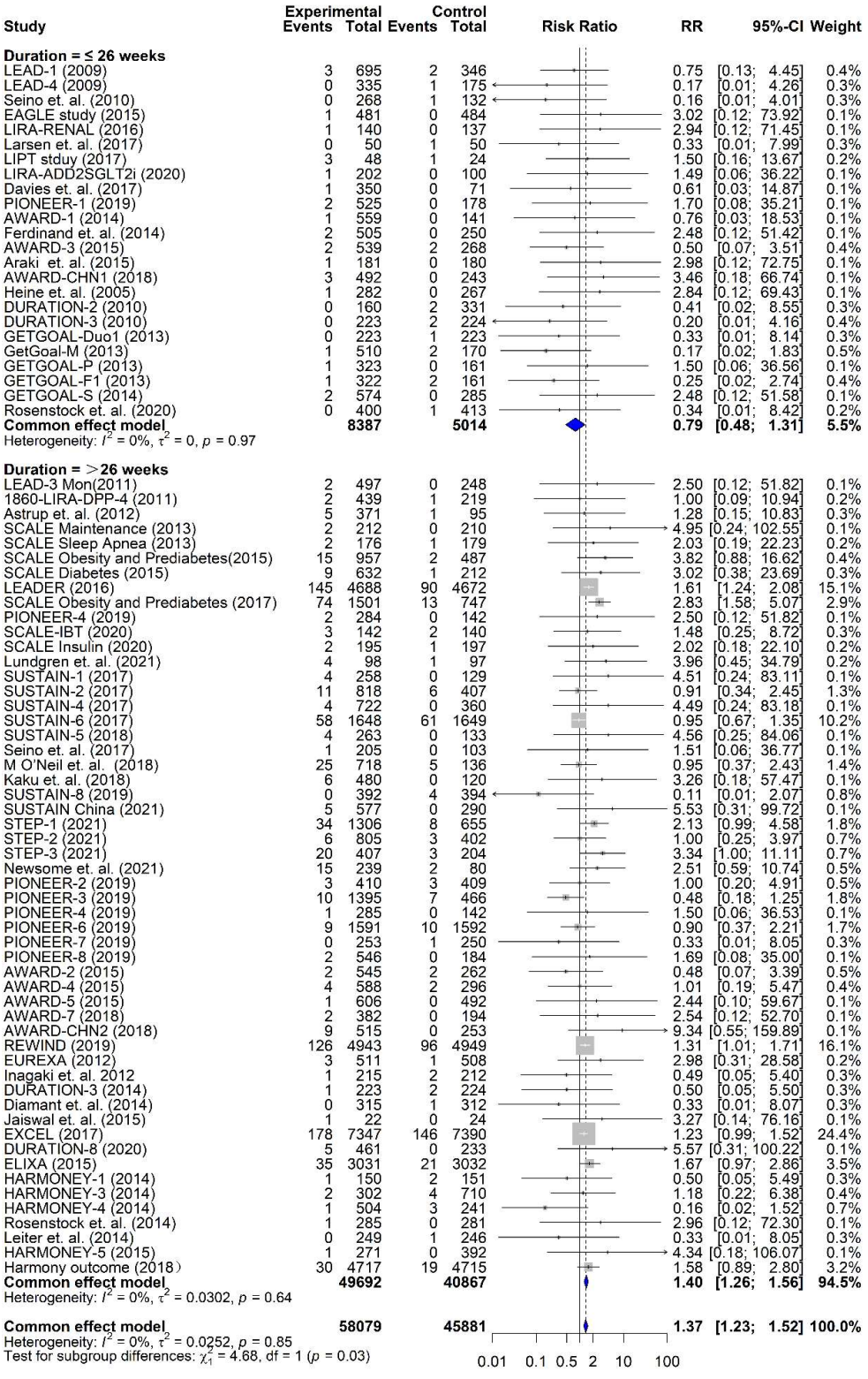
eFigure 12. Effects of doses and duration of treatment on the association between GLP-1RAs and gallbladder or biliary diseases in all included trials

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. **Abbreviations:** RR, relative risks; CI, confidential intervals; GLP-1RAs, glucagon-like peptide 1 receptor agonists; BMI, body mass index.

eFigure 12A. Effects of doses of GLP-1RAs treatments in all trials



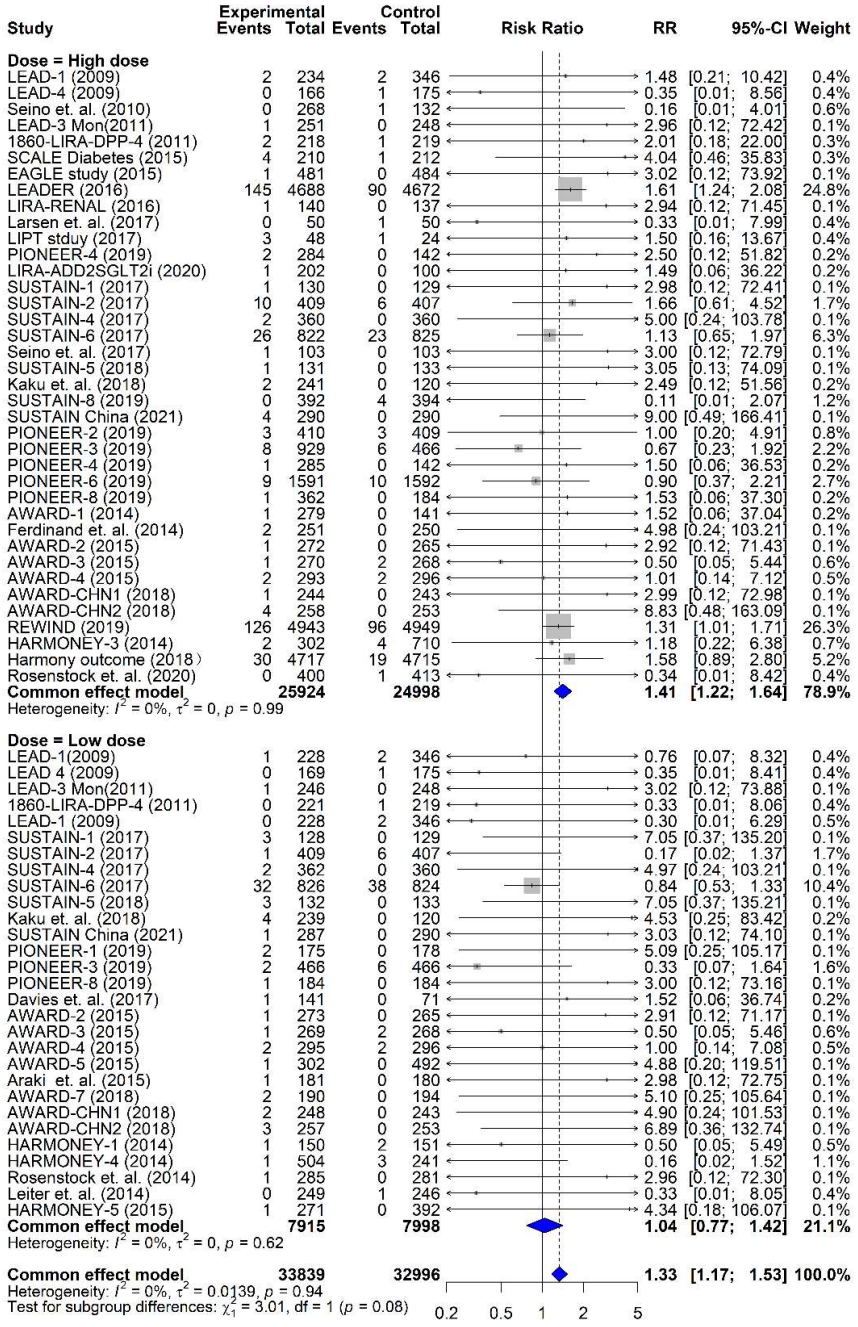
eFigure 12B . Effects of duration of GLP-1RAs treatments in all trials



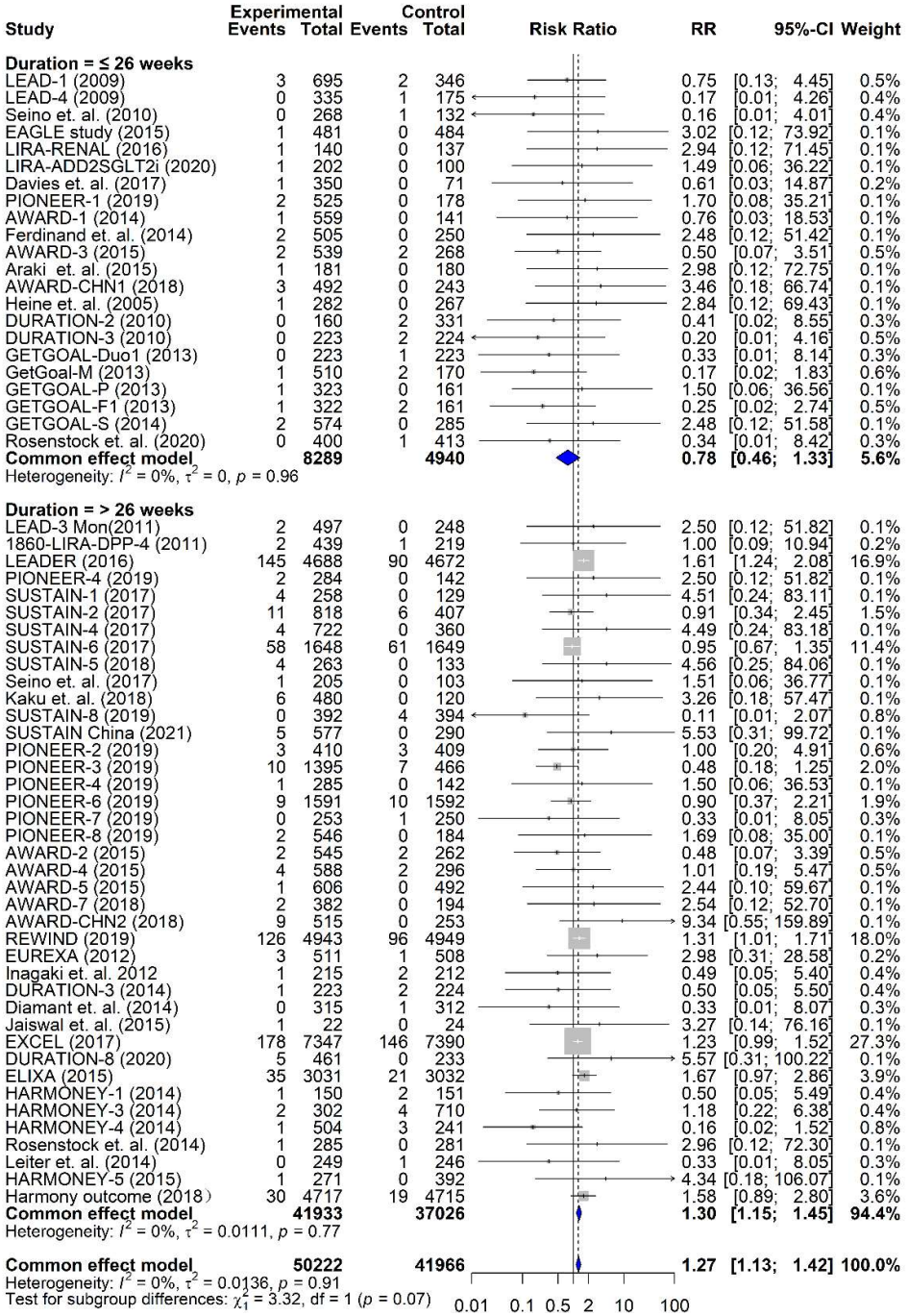
eFigure 13. Effects of doses and duration of treatment on the risks of gallbladder or biliary diseases in trials with treatment for diabetes

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risks; CI, confidential intervals.

eFigure 13A. Effects of doses of GLP-1RAs treatments in trials with treatment for diabetes



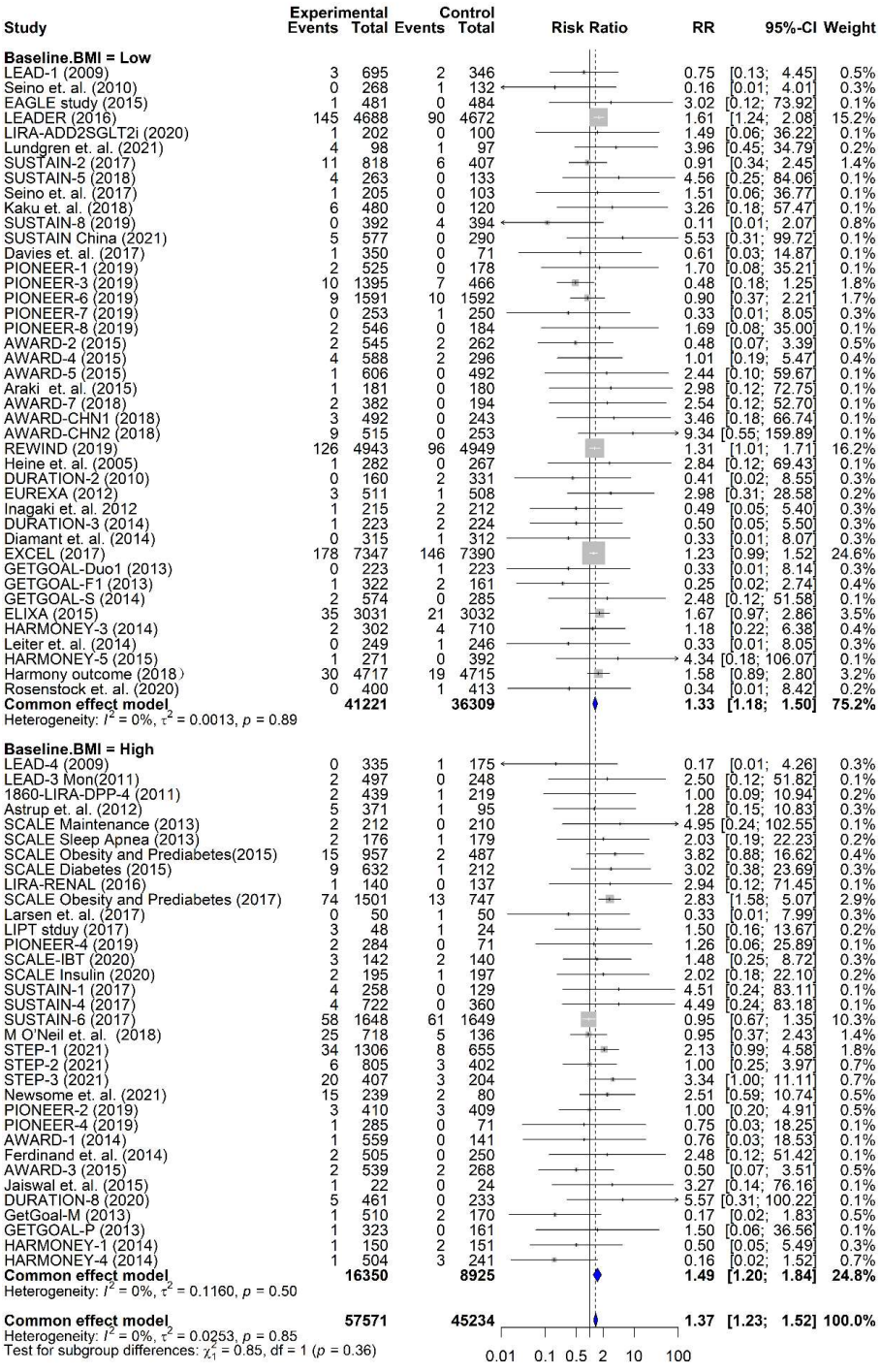
eFigure 13B. Effects of duration of GLP-1RAs treatments in trials with treatment for diabetes



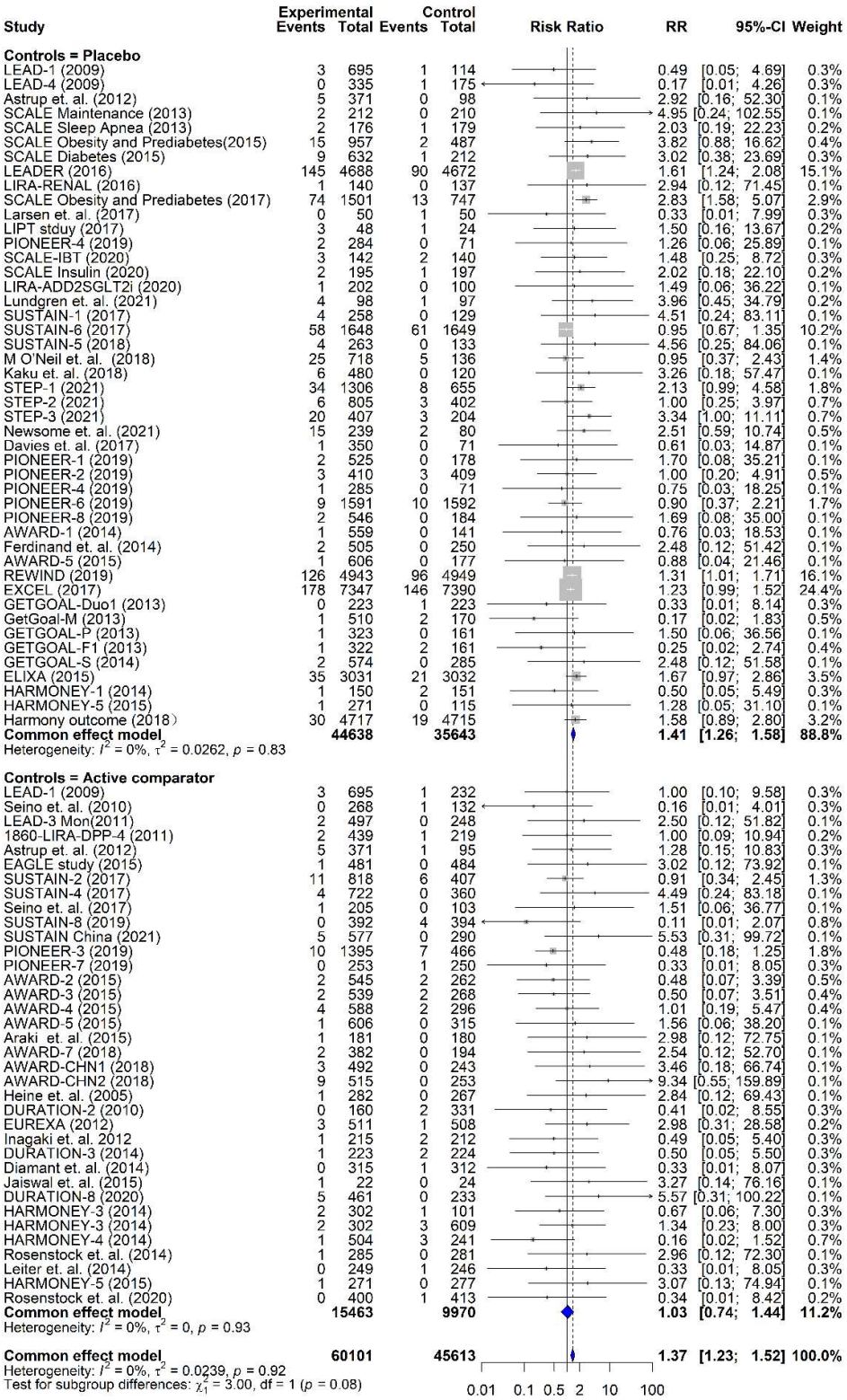
eFigure 14. Effects of baseline BMI and types of control on the association between GLP-1RAs and gallbladder or biliary diseases

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risks; CI, confidential intervals; BMI, body mass index.

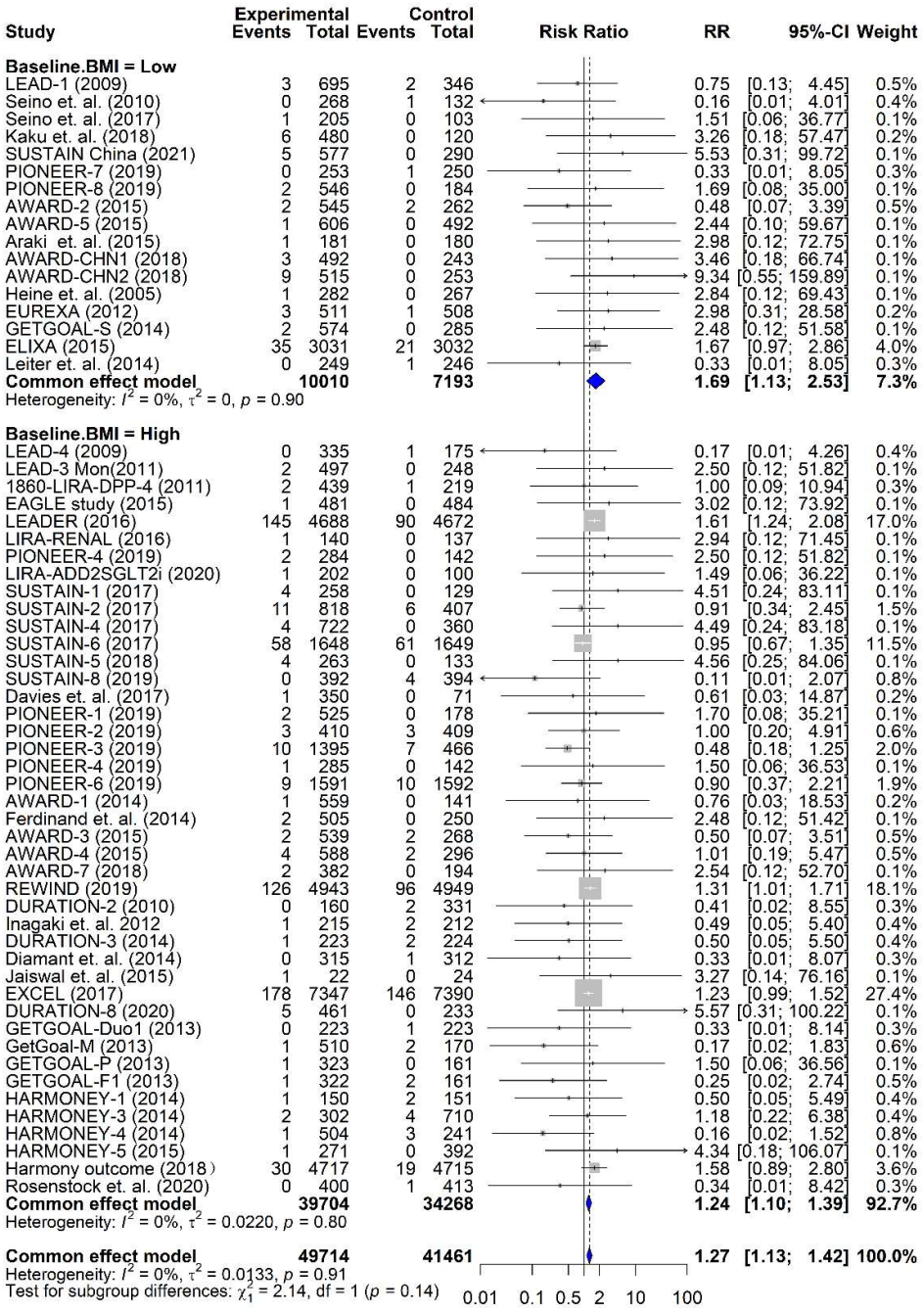
eFigure 15A. Effects of baseline BMI in all trials



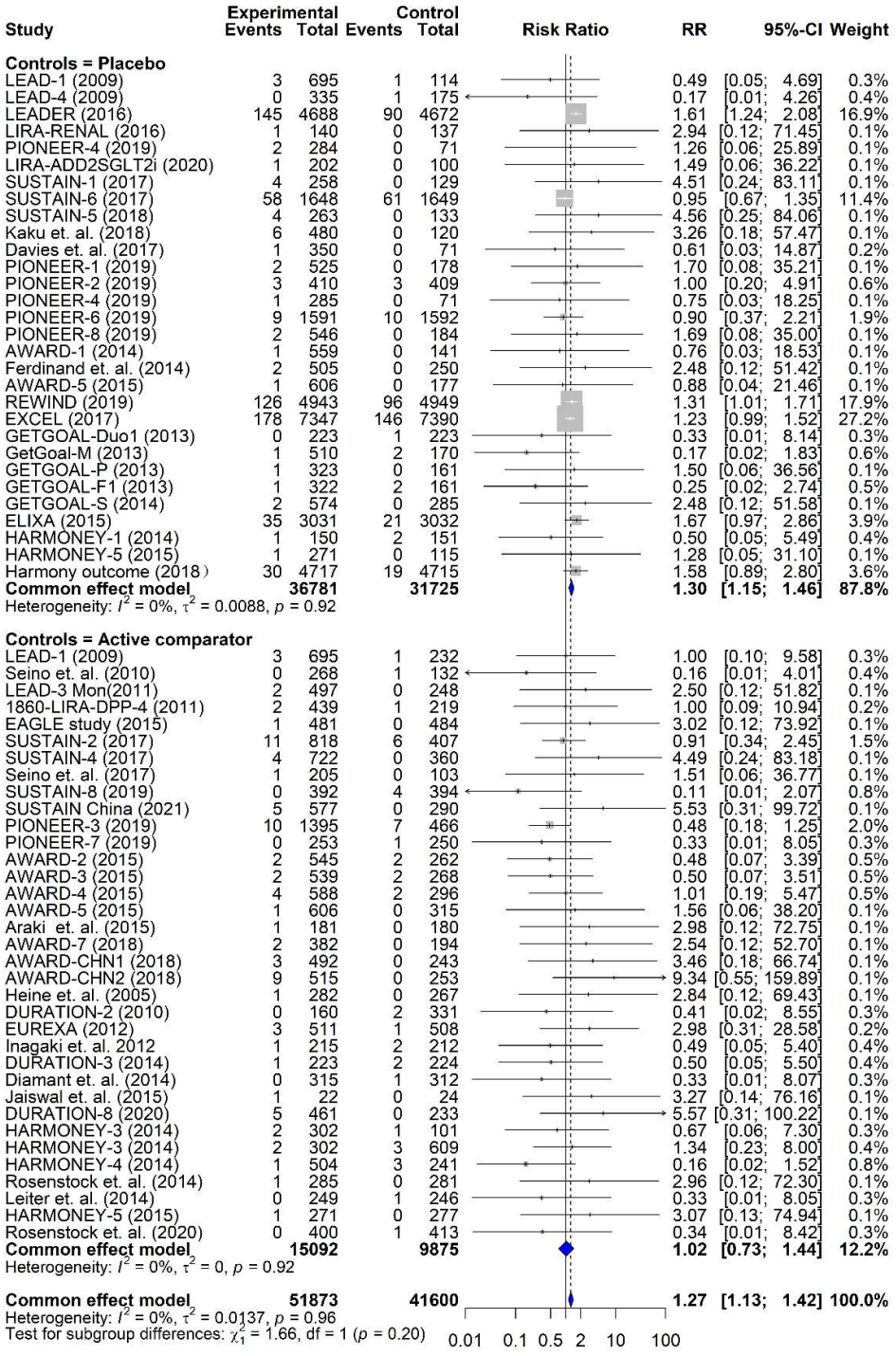
eFigure 14B. Effects of types of control in all trials



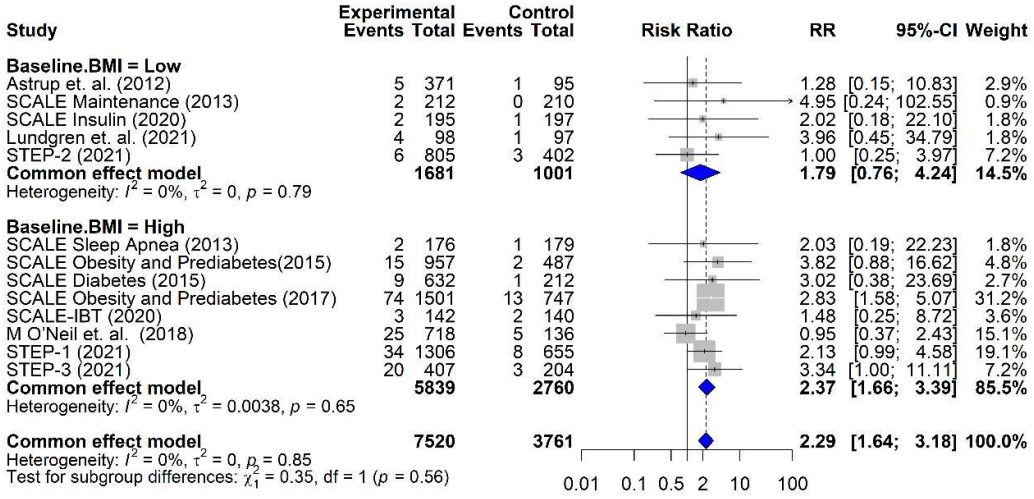
eFigure 14C. Effects of baseline BMI in trials with treatment for diabetes



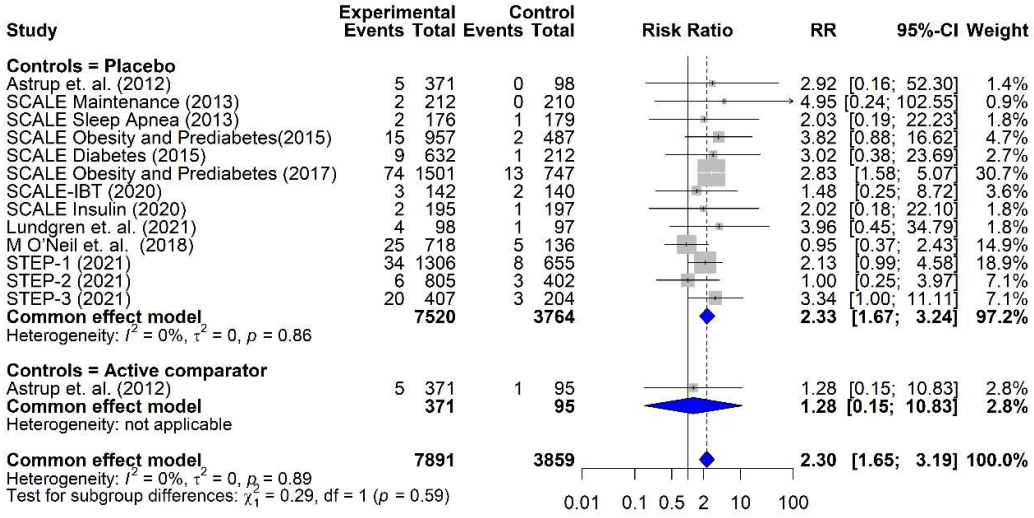
eFigure 14D. Effects of types of control in trials with treatment for diabetes



eFigure 14E. Effects of baseline BMI in trials with treatment for weight loss

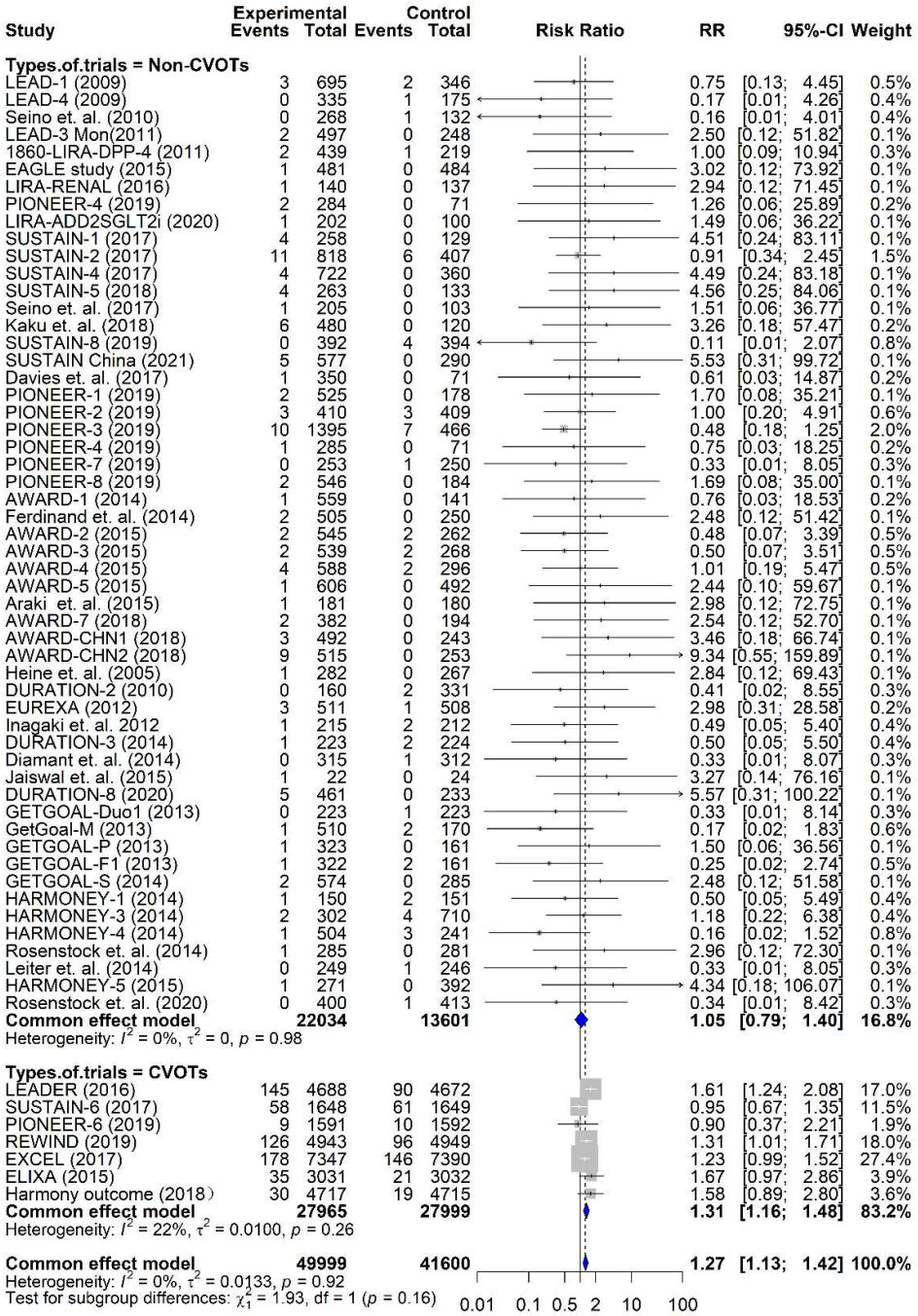


eFigure 14F. Effects of types of control in trials with treatment for weight loss



eFigure 15. Effects of types of trials on the risks of gallbladder or biliary diseases in trials with treatment for diabetes

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risks; CI, confidential intervals.

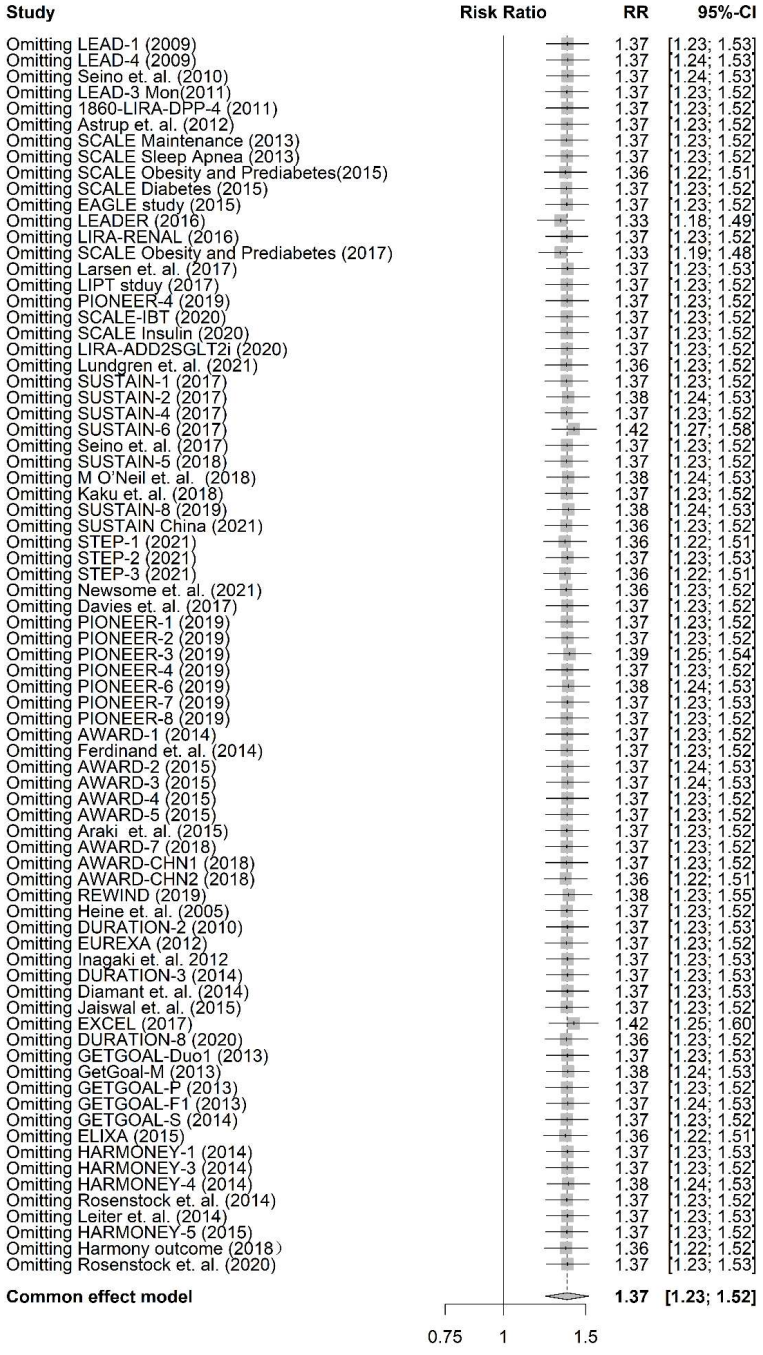


eFigure 16. Sensitivity analyses by omitting each trial one by one and removing studies with albiglutide

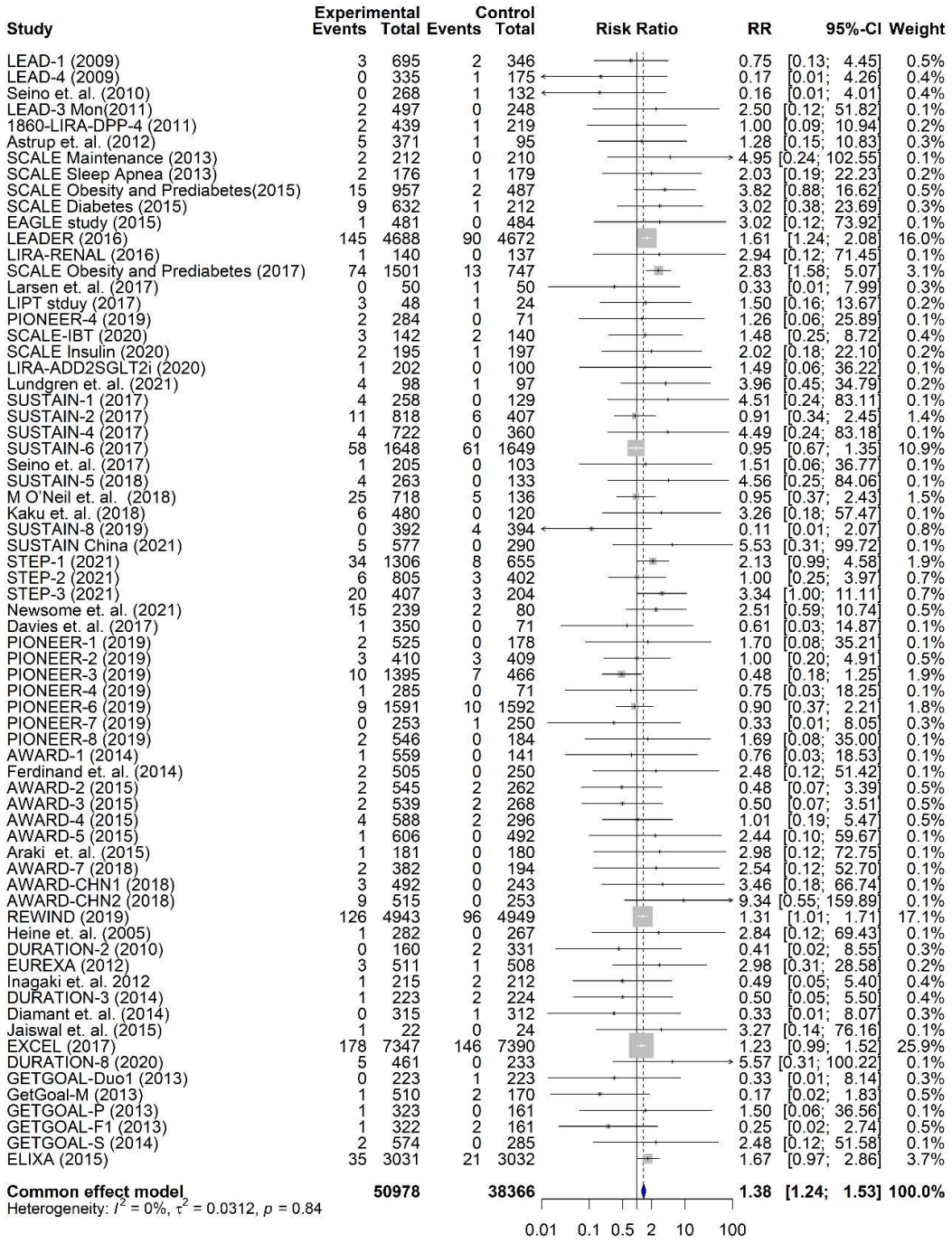
Abbreviations: GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval

Experimental, GLP-1RAs treatments; Control, placebo or active control.

eFigure 17A. Sensitivity analysis by omitting each trial one by one



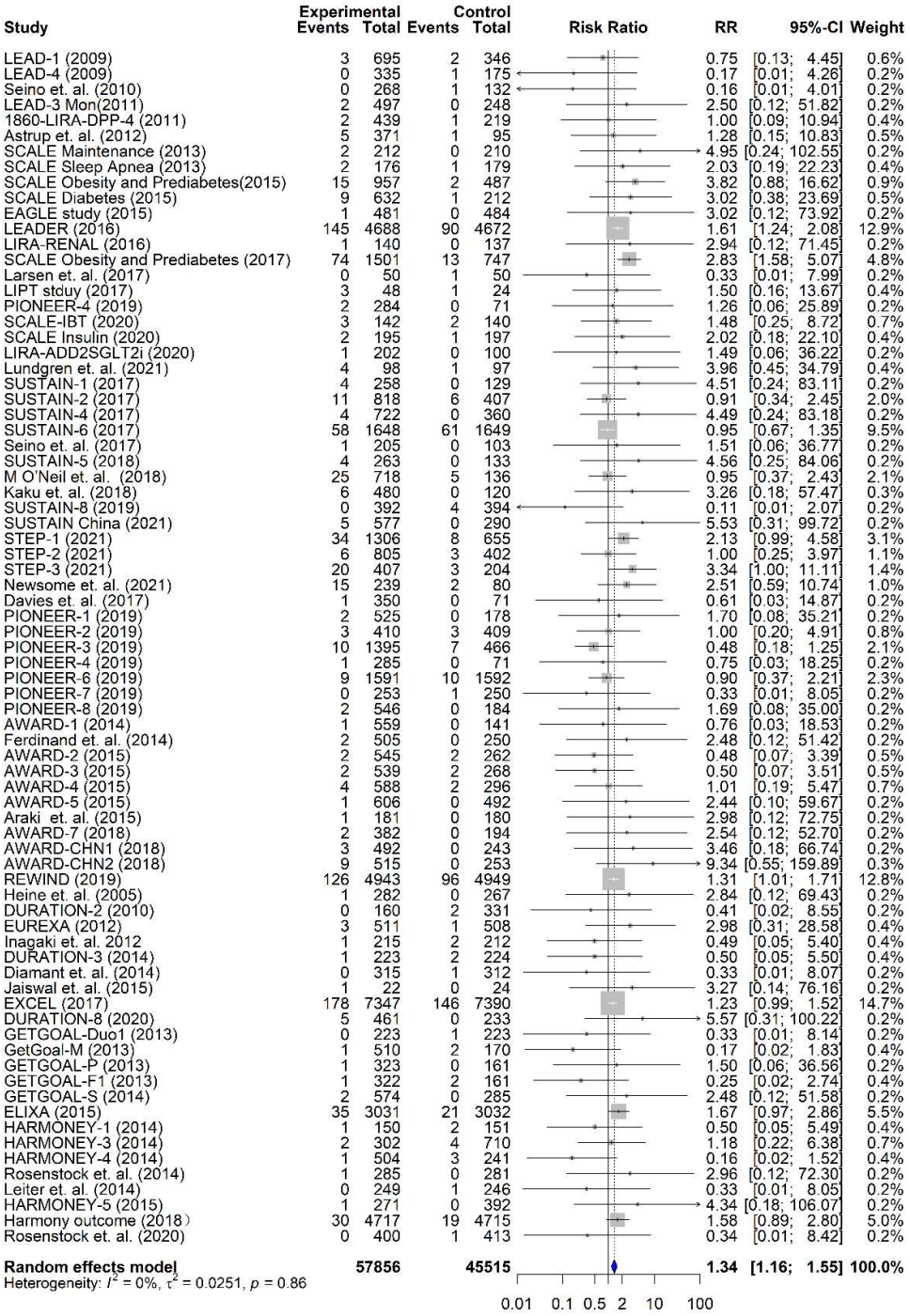
eFigure 16B. Sensitivity analysis by removing studies with albiglutide



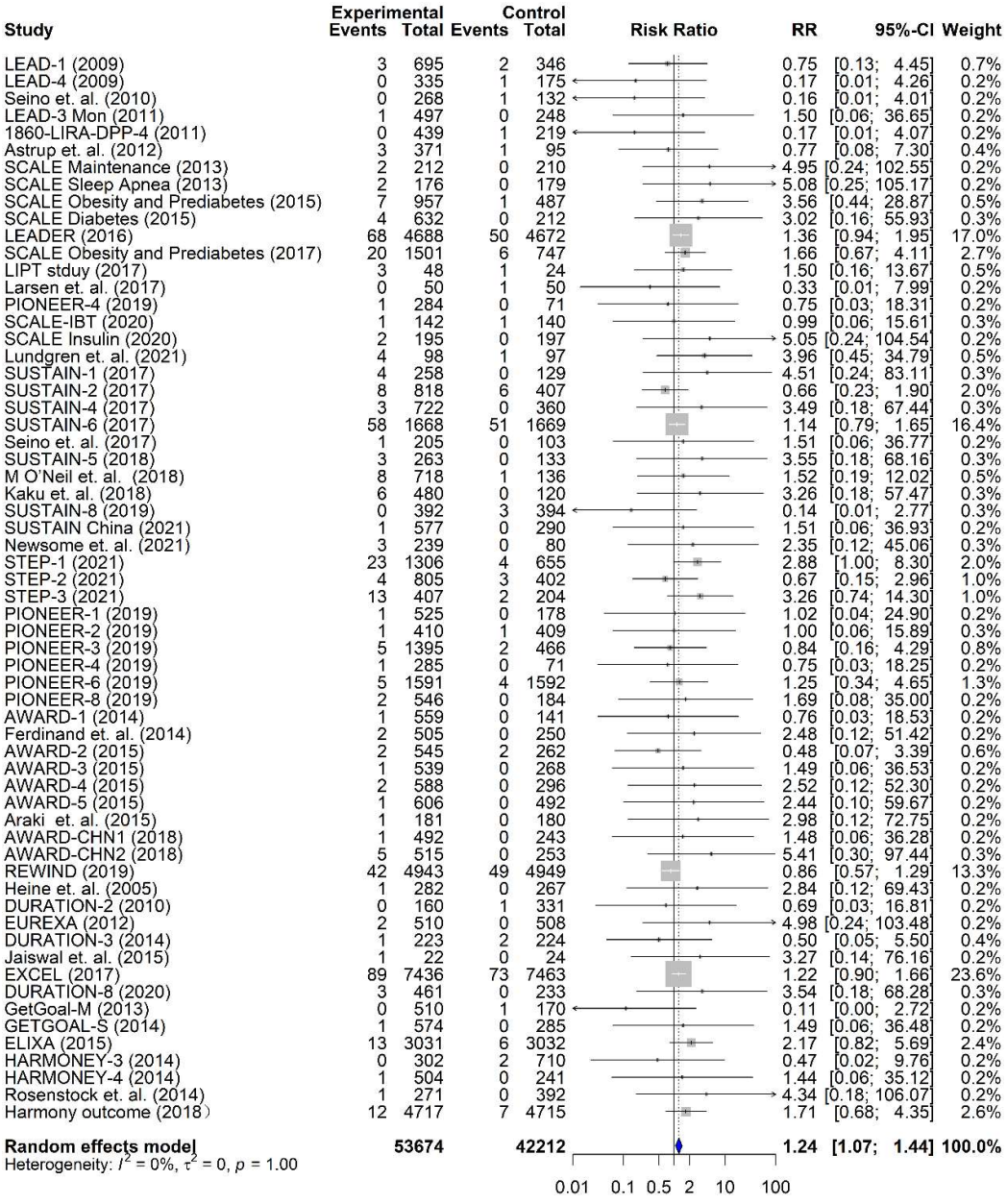
eFigure 17. Sensitivity analyses by using random-effect models

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

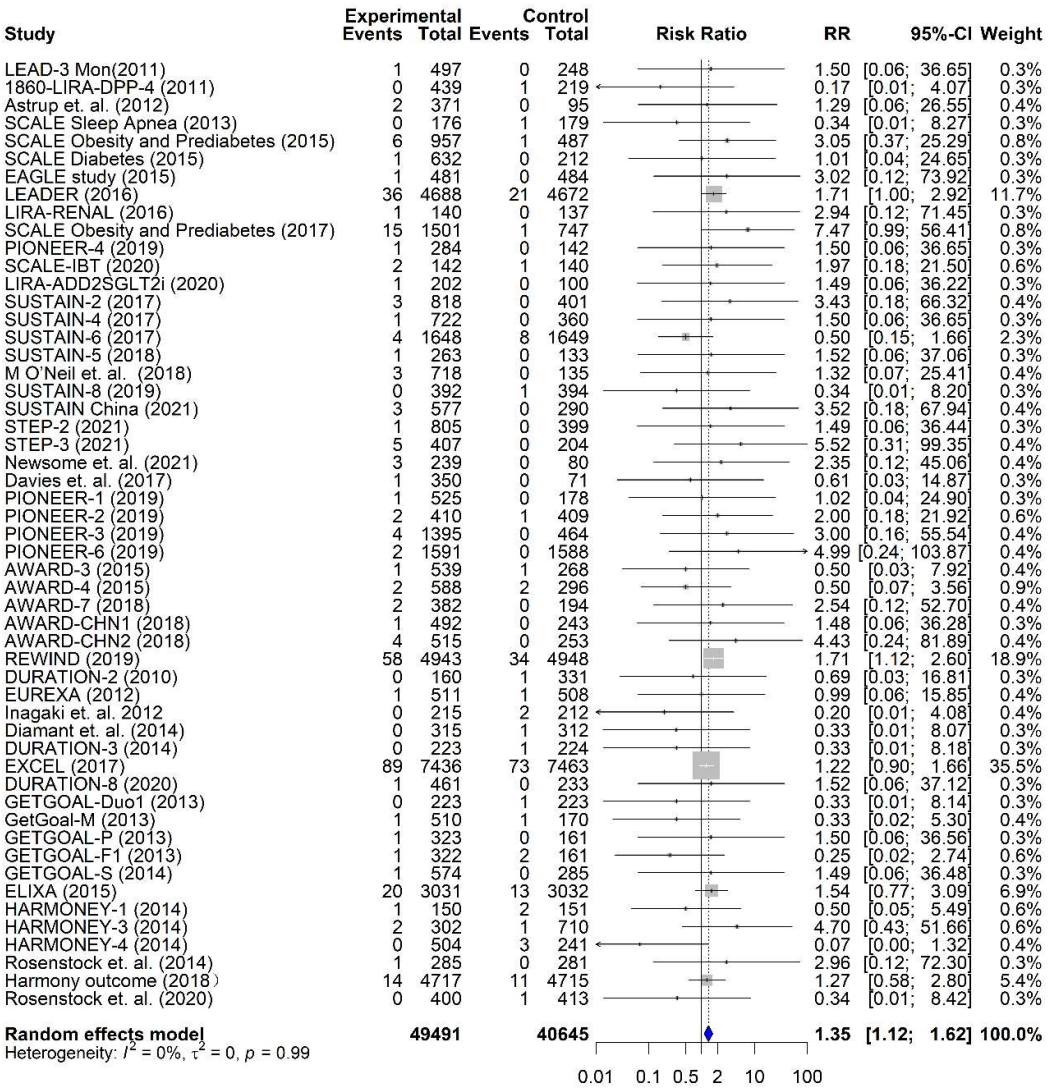
eFigure 17A. Risks of the composite of gallbladder or biliary diseases with GLP-1RAs treatments compared with controls by using random-effect models



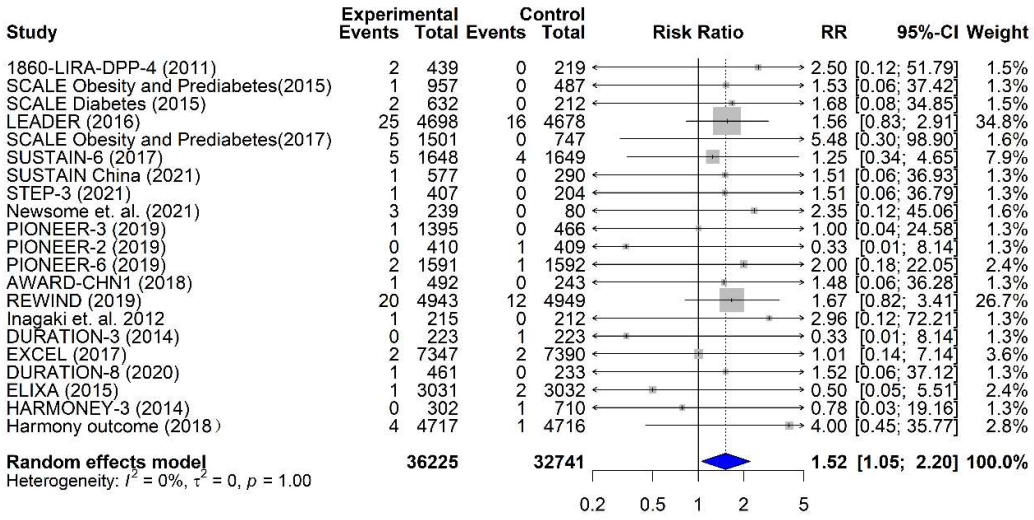
eFigure 17B. Risks of cholelithiasis with GLP-1RAs treatments compared with controls by using random-effect models



eFigure 17C. Risks of cholecystitis with GLP-1RAs treatments compared with controls by using random-effect models



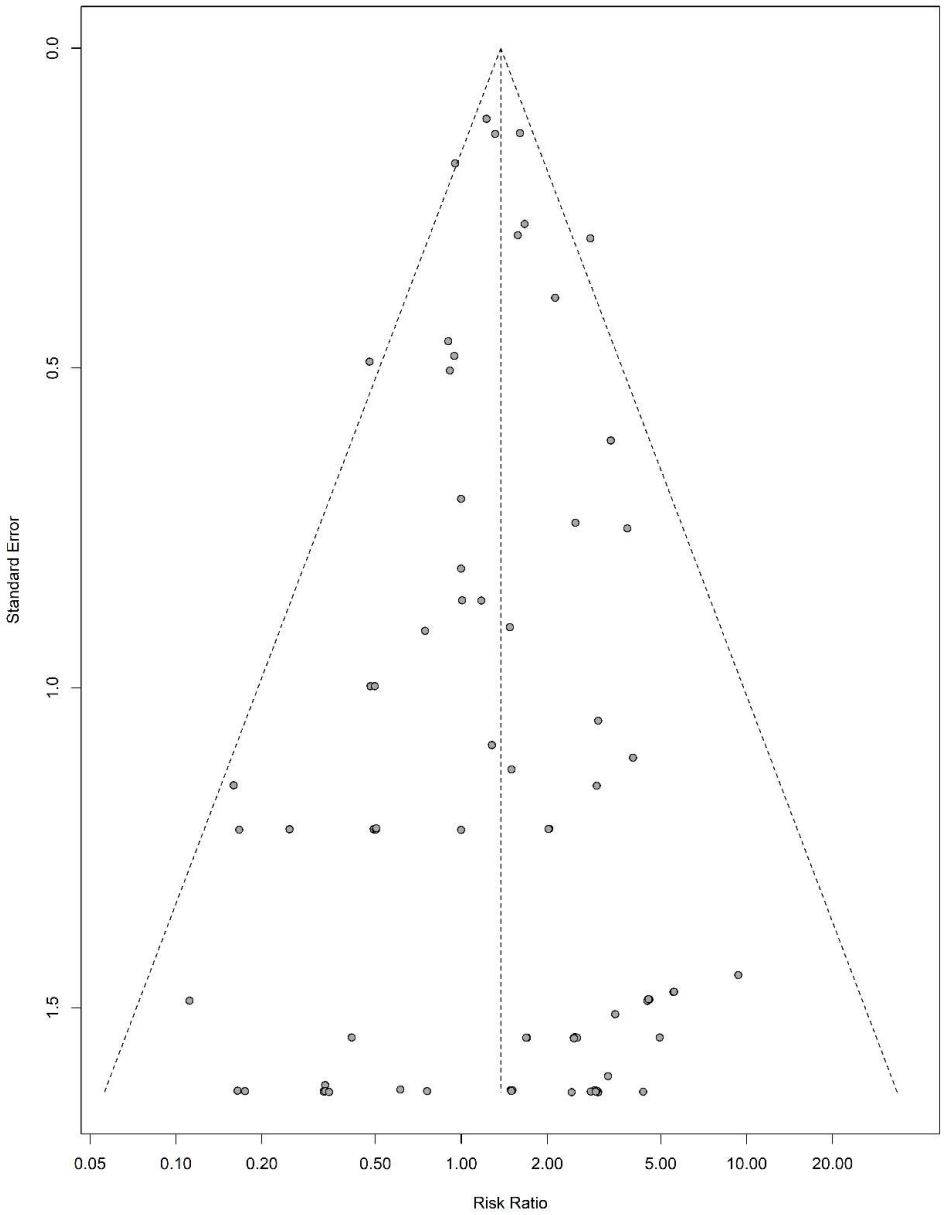
eFigure 17D. Risks of biliary diseases with GLP-1RAs treatments by using random-effect models



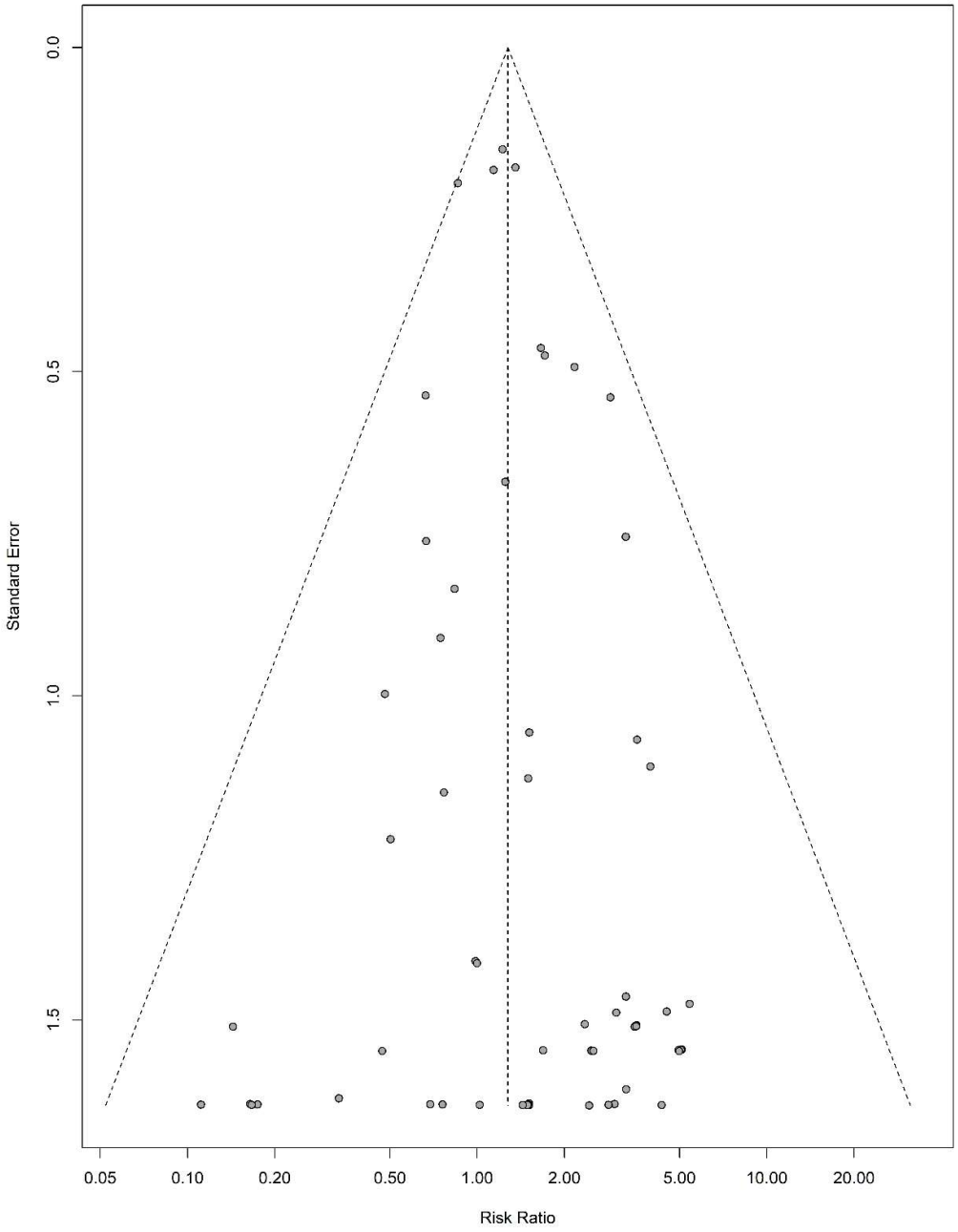
eFigure 18. Funnel plots

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

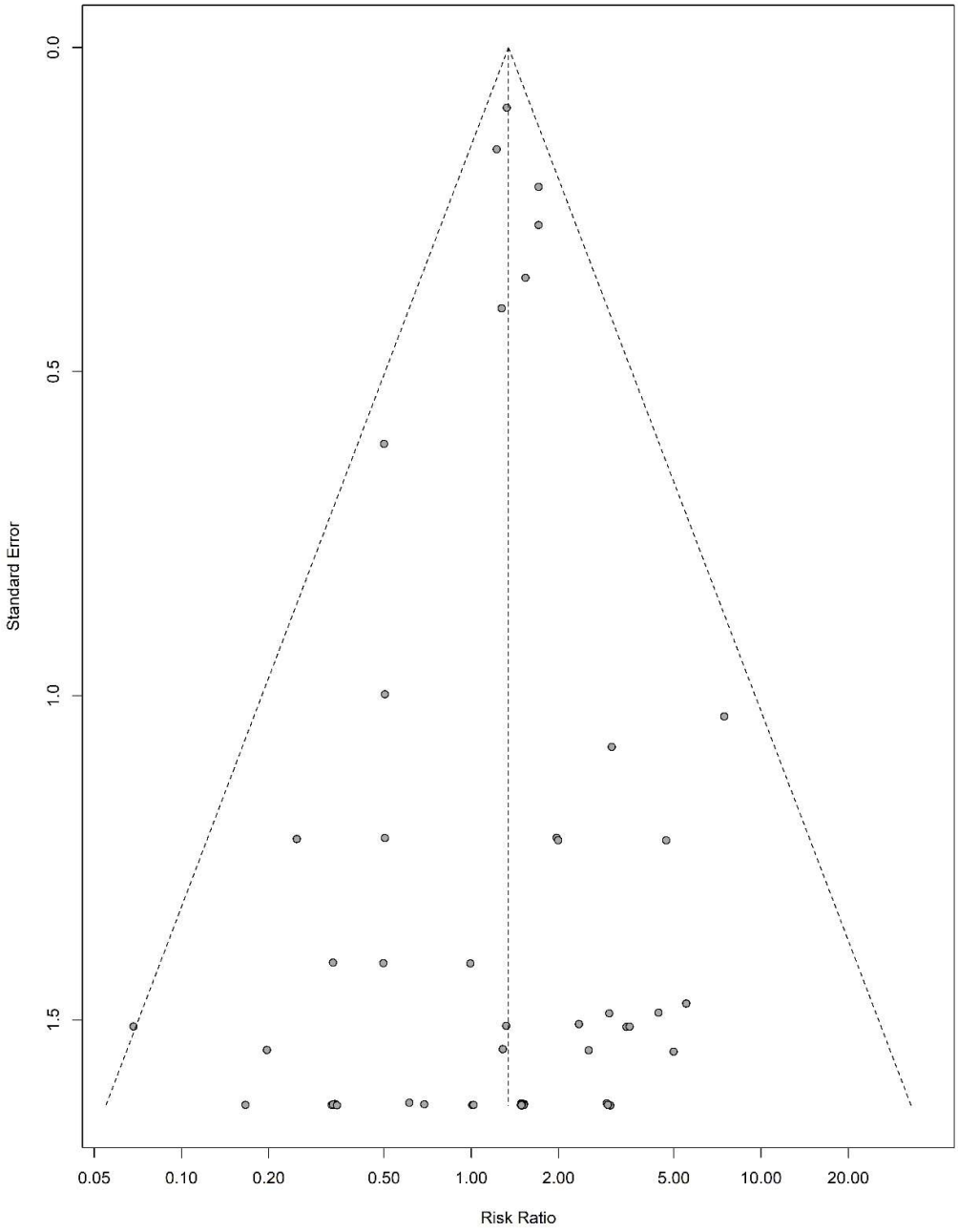
eFigure 19A. Funnel plot of studies included for the association between GLP-1RAs and the risks of gallbladder or biliary diseases



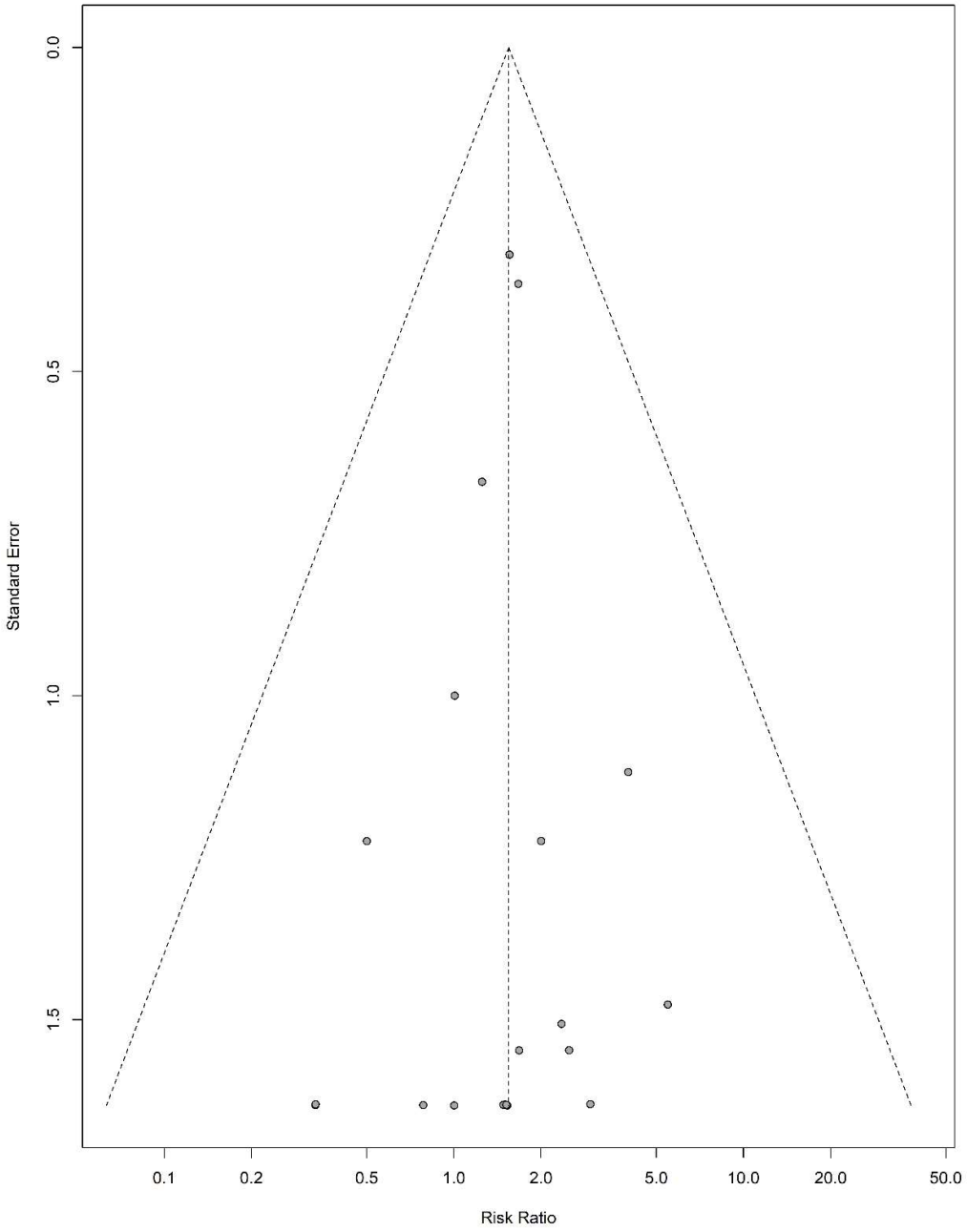
eFigure 18B. Funnel plot of studies included for the association between GLP-1RAs and the risks of cholelithiasis



eFigure 18C. Funnel plot of studies included for the association between GLP-1RAs and the risks of cholecystitis



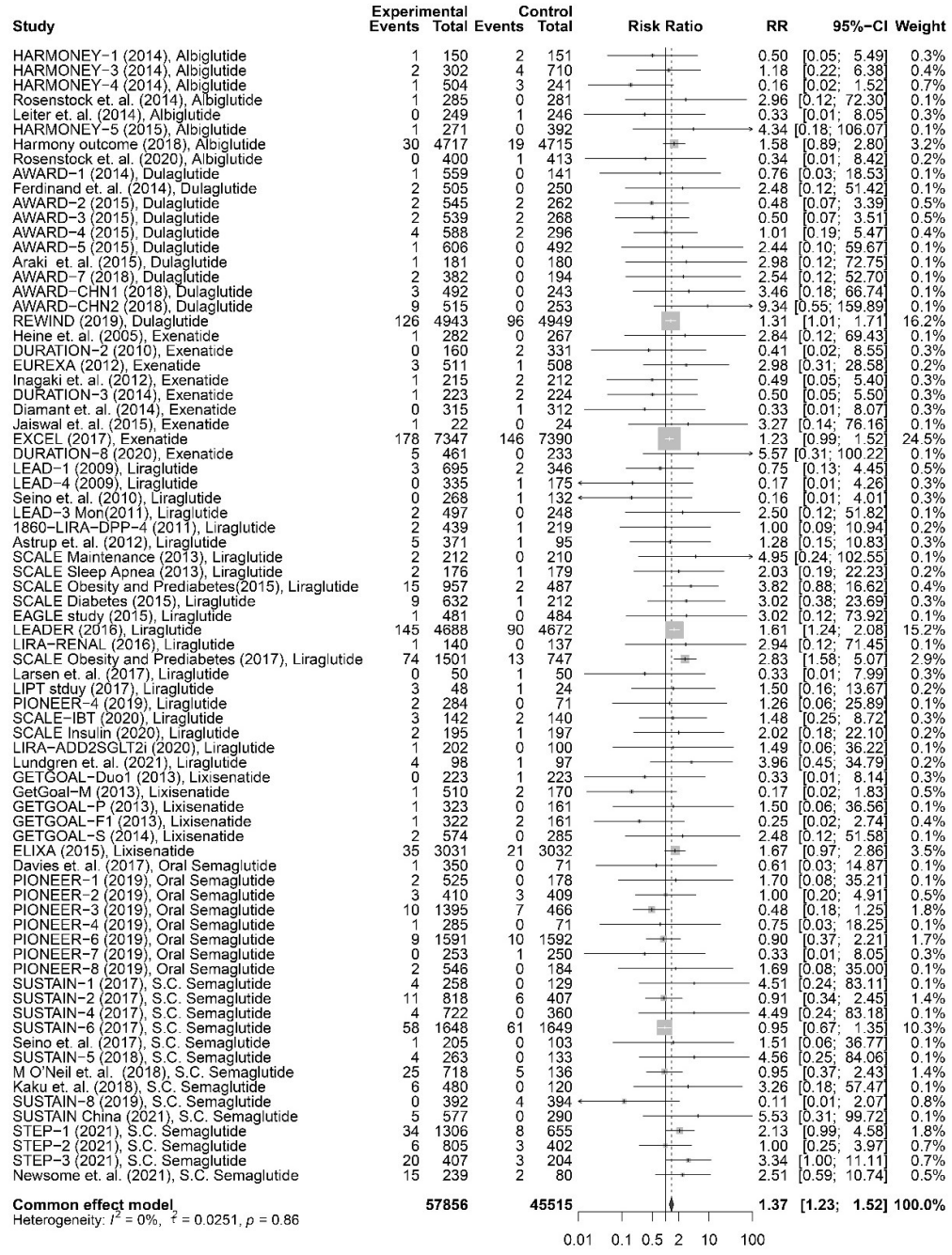
eFigure 18D. Funnel plot of studies included for the association between GLP-1RAs and the risks of biliary diseases



eResults. Risks of gallbladder or biliary diseases in patients with GLP-1RAs treatments compared with controls in all trials

Abbreviations: RR, relative risk; CI, confidence intervals. Experimental, GLP-1RA treatments;

Control, placebo or active control.



eReferences

1. Marre M, Shaw J, Braendle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabetic Medicine*. Mar 2009;26(3):268-278. doi:10.1111/j.1464-5491.2009.02666.x
2. Zinman B, Gerich J, Buse JB, et al. Efficacy and Safety of the Human Glucagon-Like Peptide-1 Analog Liraglutide in Combination With Metformin and Thiazolidinedione in Patients With Type 2 Diabetes (LEAD-4 Met+TZD). *Diabetes Care*. Jul 2009;32(7):1224-1230. doi:10.2337/dc08-2124
3. Seino Y, Rasmussen MF, Nishida T, Kaku K. Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. *Curr Med Res Opin*. May 2010;26(5):1013-22. doi:10.1185/03007991003672551
4. Garber A, Henry RR, Ratner R, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. *Diabetes Obesity & Metabolism*. Apr 2011;13(4):348-356. doi:10.1111/j.1463-1326.2010.01356.x
5. Pratley R, Nauck M, Bailey T, et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. *International Journal of Clinical Practice*. Apr 2011;65(4):397-407. doi:10.1111/j.1742-1241.2011.02656.x
6. Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *International Journal of Obesity*. Jun 2012;36(6):843-854. doi:10.1038/ijo.2011.158
7. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study. *International Journal of Obesity*. Nov 2013;37(11):1443-1451. doi:10.1038/ijo.2013.120
8. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *International Journal of Obesity*. Aug 2016;40(8):1310-1319. doi:10.1038/ijo.2016.52
9. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *The New England journal of medicine*. Jul 2 2015;373(1):11-22. doi:10.1056/NEJMoa1411892
10. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes The SCALE Diabetes Randomized Clinical Trial. *Jama-Journal of the American Medical Association*. Aug 18 2015;314(7):687-699. doi:10.1001/jama.2015.9676
11. D'Alessio D, Häring HU, Charbonnel B, et al. Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. *Diabetes Obes Metab*. Feb 2015;17(2):170-8. doi:10.1111/dom.12406
12. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. Jul 28 2016;375(4):311-322. doi:10.1056/NEJMoa1603827
13. Davies MJ, Bain SC, Atkin SL, et al. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. *Diabetes Care*. Feb 2016;39(2):222-230.

doi:10.2337/dc14-2883
14. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. Apr 8 2017;389(10077):1399-1409. doi:10.1016/s0140-6736(17)30069-7
15. Larsen JR, Vedtofte L, Jakobsen MSL, et al. Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder A Randomized Clinical Trial. *Jama Psychiatry*. Jul 2017;74(7):719-728. doi:10.1001/jamapsychiatry.2017.1220
16. Frossing S, Nylander M, Chabanova E, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. *Diabetes Obesity & Metabolism*. Jan 2018;20(1):215-218. doi:10.1111/dom.13053
17. Wadden TA, Tronieri JS, Sugimoto D, et al. Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for Obesity in Primary Care: The SCALE IBT Randomized Controlled Trial. *Obesity (Silver Spring, Md)*. Mar 2020;28(3):529-536. doi:10.1002/oby.22726
18. Garvey WT, Birkenfeld AL, Dicker D, et al. Efficacy and Safety of Liraglutide 3.0 mg in Individuals With Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin Randomized Controlled Trial. *Diabetes Care*. May 2020;43(5):1085-1093. doi:10.2337/dc19-1745
19. Deshmukh V, Blonde L, Belousova L, et al. Liraglutide as add-on to sodium-glucose cotransporter-2 inhibitors in patients with inadequately controlled type 2 diabetes (LIRA-ADD2SGLT2i): A 26-week, randomized, double-blind, placebo-controlled trial. Conference Abstract. *Indian Journal of Endocrinology and Metabolism*. 2019;23(7):S16-S17.
20. Lundgren JR, Janus C, Jensen SBK, et al. Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined. *New England Journal of Medicine*. May 6 2021;384(18):1719-1730. doi:10.1056/NEJMoa2028198
21. Sorli C, Harashima S-i, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes & Endocrinology*. Apr 2017;5(4):251-260. doi:10.1016/s2213-8587(17)30013-x
22. Ahren B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes & Endocrinology*. May 2017;5(5):341-354. doi:10.1016/s2213-8587(17)30092-x
23. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes & Endocrinology*. May 2017;5(5):355-366. doi:10.1016/s2213-8587(17)30085-2
24. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England journal of medicine*. Nov 10 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141
25. Seino Y, Terauchi Y, Osonoi T, et al. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes. *Diabetes Obes Metab*. Feb 2018;20(2):378-388. doi:10.1111/dom.13082

26. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial. *Journal of Clinical Endocrinology & Metabolism*. Jun 2018;103(6):2291-2301. doi:10.1210/jc.2018-00070
27. O'Neil PM, Birkenfeld AL, McGowan B, et al. A randomized, phase II, placebo- and active-controlled dose-ranging study of semaglutide for treatment of obesity in subjects without diabetes. Conference Abstract. *Endocrine Reviews*. 2018;39(2)
28. Kaku K, Yamada Y, Watada H, et al. Safety and efficacy of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: A randomized trial. *Diabetes Obes Metab*. May 2018;20(5):1202-1212. doi:10.1111/dom.13218
29. Lingvay I, Catarig A-M, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes & Endocrinology*. Nov 2019;7(11):834-844. doi:10.1016/s2213-8587(19)30311-0
30. Ji L, Xiaolin D, Eliaschewitz F, et al. Efficacy and safety of once-weekly semaglutide vs. once-daily sitagliptin as add-on to metformin in subjects with type 2 diabetes (SUSTAIN China MRCT): A 30-week double-blind, phase 3a, randomised trial. Conference Abstract. *Diabetes*. 2020;69doi:10.2337/db20-961-P
31. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *The New England journal of medicine*. Mar 18 2021;384(11):989. doi:10.1056/NEJMoa2032183
32. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Article. *The Lancet*. 2021;397(10278):971-984. doi:10.1016/S0140-6736(21)00213-0
33. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: the STEP 3 Randomized Clinical Trial. Clinical Trial, Phase III; Comparative Study; Journal Article; Randomized Controlled Trial. *JAMA*. 2021;325(14):1403-1413. doi:10.1001/jama.2021.1831
34. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *The New England journal of medicine*. Mar 25 2021;384(12):1113-1124. doi:10.1056/NEJMoa2028395
35. Davies M, Pieber TR, Hartoft-Nielsen M-L, Hansen OKH, Jabbour S, Rosenstock J. Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes A Randomized Clinical Trial. *Jama-Journal of the American Medical Association*. Oct 17 2017;318(15):1460-1470. doi:10.1001/jama.2017.14752
36. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. Article. *Diabetes Care*. 2019;42(9):1724-1732. doi:10.2337/dc19-0749
37. Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care*. Dec 2019;42(12):2272-2281. doi:10.2337/dc19-0883
38. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea The PIONEER 3 Randomized Clinical Trial. *Jama-Journal of the American*

Medical Association. Apr 16 2019;321(15):1466-1480. doi:10.1001/jama.2019.2942
39. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet*. Jul 6 2019;394(10192):39-50. doi:10.1016/s0140-6736(19)31271-1
40. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England journal of medicine*. Aug 29 2019;381(9):841-851. doi:10.1056/NEJMoa1901118
41. Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *Lancet Diabetes & Endocrinology*. Jul 2019;7(7):528-539. doi:10.1016/s2213-8587(19)30194-9
42. Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. *Diabetes Care*. Dec 2019;42(12):2262-2271. doi:10.2337/dc19-0898
43. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care*. Aug 2014;37(8):2159-67. doi:10.2337/dc13-2760
44. Ferdinand KC, White WB, Calhoun DA, et al. Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. *Hypertension*. Oct 2014;64(4):731-7. doi:10.1161/hypertensionaha.114.03062
45. Giorgino F, Benroubi M, Sun J-H, Zimmermann AG, Pechtner V. Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2). *Diabetes Care*. Dec 2015;38(12):2241-2249. doi:10.2337/dc14-1625
46. Umpierrez G, Povedano ST, Manghi FP, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Article. *Diabetes Care*. 2014;37(8):2168-2176. doi:10.2337/dc13-2759
47. Reaney M, Yu M, Van Brunt K, Milicevic Z, Hayes C. Patient-reported outcomes with once-weekly dulaglutide vs. Insulin glargine, both in combination with premeal insulin lispro, in type 2 diabetes mellitus (AWARD-4). Conference Abstract. *Diabetes*. 2014;63:A607. doi:10.2337/db14-2344-2488
48. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. Aug 2014;37(8):2149-58. doi:10.2337/dc13-2761
49. Araki E, Inagaki N, Tanizawa Y, Oura T, Takeuchi M, Imaoka T. Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. *Diabetes Obes Metab*. Oct 2015;17(10):994-1002. doi:10.1111/dom.12540
50. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. Aug 2018;6(8):605-617. doi:10.1016/s2213-8587(18)30104-9
51. Chen YH, Huang CN, Cho YM, et al. Efficacy and safety of dulaglutide monotherapy compared

with glimepiride in East-Asian patients with type 2 diabetes in a multicentre, double-blind, randomized, parallel-arm, active comparator, phase III trial. *Diabetes Obes Metab*. Sep 2018;20(9):2121-2130. doi:10.1111/dom.13340

52. Wang W, Nevárez L, Filippova E, et al. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in mainly Asian patients with type 2 diabetes mellitus on metformin and/or a sulphonylurea: A 52-week open-label, randomized phase III trial. *Diabetes Obes Metab*. Feb 2019;21(2):234-243. doi:10.1111/dom.13506

53. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. Jul 13 2019;394(10193):121-130. doi:10.1016/s0140-6736(19)31149-3

54. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. Oct 18 2005;143(8):559-69. doi:10.7326/0003-4819-143-8-200510180-00006

55. Bergenstal RM, Wysham C, MacConell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet*. Aug 7 2010;376(9739):431-439. doi:10.1016/s0140-6736(10)60590-9

56. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet*. Jun 16 2012;379(9833):2270-8. doi:10.1016/s0140-6736(12)60479-6

57. Inagaki N, Atsumi Y, Oura T, Saito H, Imaoka T. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. *Clin Ther*. Sep 2012;34(9):1892-908.e1. doi:10.1016/j.clinthera.2012.07.007

58. Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. *Lancet Diabetes Endocrinol*. Jun 2014;2(6):464-73. doi:10.1016/s2213-8587(14)70029-4

59. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care*. Oct 2014;37(10):2763-73. doi:10.2337/dc14-0876

60. Jaiswal M, Martin CL, Brown MB, et al. Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study. *J Diabetes Complications*. Nov-Dec 2015;29(8):1287-94. doi:10.1016/j.jdiacomp.2015.07.013

61. Frias JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes & Endocrinology*. Dec 2016;4(12):1004-1016. doi:10.1016/s2213-8587(16)30267-4

62. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. Sep 28 2017;377(13):1228-1239. doi:10.1056/NEJMoa1612917

63. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). *Diabetes Care*. Sep 2013;36(9):2497-503. doi:10.2337/dc12-2462
64. Ahrén B, Leguizamo Dimas A, Miossec P, Saubadu S, Aronson R. Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin (GetGoal-M). *Diabetes Care*. Sep 2013;36(9):2543-50. doi:10.2337/dc12-2006
65. Rosenstock J, Hanefeld M, Shamanna P, et al. Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). *J Diabetes Complications*. May-Jun 2014;28(3):386-92. doi:10.1016/j.jdiacomp.2014.01.012
66. Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). *Diabetes Obes Metab*. Nov 2013;15(11):1000-7. doi:10.1111/dom.12121
67. Bolli GB, Munteanu M, Dotsenko S, et al. Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). *Diabetic medicine : a journal of the British Diabetic Association*. Feb 2014;31(2):176-84. doi:10.1111/dme.12328
68. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *The New England journal of medicine*. Dec 3 2015;373(23):2247-57. doi:10.1056/NEJMoa1509225
69. Reusch J, Stewart MW, Perkins CM, et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. *Diabetes Obes Metab*. Dec 2014;16(12):1257-64. doi:10.1111/dom.12382
70. Ahrén B, Johnson SL, Stewart M, et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care*. Aug 2014;37(8):2141-8. doi:10.2337/dc14-0024
71. Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia*. Dec 2014;57(12):2475-84. doi:10.1007/s00125-014-3360-3
72. Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care*. Aug 2014;37(8):2317-25. doi:10.2337/dc14-0001
73. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. *Diabetes Care*. Oct 2014;37(10):2723-30. doi:10.2337/dc13-2855
74. Home PD, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and

glimepiride: HARMONY 5. *Diabetes Obes Metab*. Feb 2015;17(2):179-87. doi:10.1111/dom.12414
75. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. Oct 27 2018;392(10157):1519-1529. doi:10.1016/s0140-6736(18)32261-x
76. Rosenstock J, Nino A, Soffer J, et al. Impact of a Weekly Glucagon-Like Peptide 1 Receptor Agonist, Albiglutide, on Glycemic Control and on Reducing Prandial Insulin Use in Type 2 Diabetes Inadequately Controlled on Multiple Insulin Therapy: A Randomized Trial. *Diabetes Care*. Oct 2020;43(10):2509-2518. doi:10.2337/dc19-2316

